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Characteristics of chronic depression

before, during and after inpatient treatment

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1 Abstract

Background

Around 20% - 30% of depressed individuals experience a chronic form of depression lasting two or more years (Arnow & Constantino, 2003; Lehmann, 1983; Gilmer et al., 2005; Wiersma, van Oppen, van Schaik, van der Does, Beekman, & Penninx, 2011). Chronic depression poses a significant burden over long stretches of time on patients, their families as well as on society as a whole. Research has focused on chronic depression in recent years. However, more research on the characteristics of chronic depression is needed to support early diagnosis and adequate treatment.

The thesis aims at gaining insights on differentiating characteristics of chronic depression compared to nonchronic depression. The focus is on clinical symptomatology, sociodemographic information, clinical and personal history, personality factors and psychiatric comorbidity as well as inpatient treatment specifics. The three guiding hypotheses specifically compare chronically and nonchronically depressed individuals based on their level of impairment, neurotic and extraverted personality styles as well as the extent of adverse childhood events.

Method

The data analyzed in the present study were collected within the scope of a multicenter trial with a prospective naturalistic setting conducted as part of the German research network on depression (Seemüller et al., 2009). In total, 1073 patients took part in the study. In the current study 954 patients with unipolar depressive disorders (ICD-10: F32, F33, F34) were included and data collected during the inpatient treatment period and at the one-year follow-up were analyzed.

Chronic depression was defined as the presence of an unipolar affective disorder for more than two years. Based on this definition 113 patients (11.8%) individuals were classified as chronically depressed.

Depression severity was assessed biweekly via the following measures: Hamilton Depression Rating Scale (HAMD) (Hamilton, 1967), Montgomery Asberg Rating Scale (MADRS) (Montgomery and Asberg, 1979), and Beck-depression-inventory (BDI) (Beck et al., 1961;

Hautzinger et al., 1994). Personality characteristics were collected at admission and discharge using the Neo-Five Factor Inventory (Neo-FFI) (Costa, P.T. & McCrae, R.R., 1992). Individual functioning was assessed via the following scales: Global Assessment of Functioning Scale (GAF) (DSM-IV, American Psychiatric Association, 2000), Social and Occupational Functioning Assessment Scale (SOFAS) (DSM-IV, American Psychiatric Association, 2000), Clinical Global Impression rating scales (CGI) (Guy, 1976). Sociodemographic, personal and clinical information were attained via the basic assessment scale of clinical and socio-demographic variables in psychiatry (BADO) (Cording et al., 1995). Fisher's exact test and t-tests were carried out to compare the groups on the measures described above. To evaluate the relative relevance of the observed variables logistic regression analyses were calculated. Repeated measurement ANOVAs were carried out to analyze change over time in clinical and personal characteristics.

Results

At admission of the inpatient stay observer-rated measures of acute depressive symptomatology (HAMD 17, MADRS) and of social and occupational functioning (GAF, SOFAS, CGI) were similar in the two groups (chronically vs. nonchronically depressed individuals) and indicated significant impairment. The two groups only differed on the self-report measure BDI and the domains neuroticism and extraversion on the NEO-FFI with chronically depressed individuals obtaining higher BDI and neuroticism scores and lower extraversion scores.

Both groups benefited strongly from the inpatient stay experiencing a significant symptom reduction on all measures (HAMD 17, MADRS, BDI, GAF, SOFAS, CGI) and positive changes in all BIG FIVE personality domains (neuroticism, extraversion, openness to experience, tolerance, conscientiousness).

However, the recovery in the group of chronically depressed individuals was not as successful and achieved with greater effort. This was evident via a longer hospital stay, a greater variety of applied medication classes, lower remission rates, increased rates of suicidal ideation as well as higher values on measures of depressive symptomatology (HAMD 17, MADRS, CGI) and lower values on social and occupational functioning (GAF, SOFAS) at discharge. Furthermore, a number of repeated measurement ANOVAS showed significant interaction effects indicating a lower rate of change for chronically depressed individuals compared to nonchronically depressed

individuals (admission and discharge data: HAMD 17, MADRS, GAF, CGI; biweekly data: MADRS). In addition, individuals with chronic depression continued to obtain higher neuroticism scores and lower extraversion scores at discharge. After the one-year follow-up depression severity was not any more significantly elevated for the chronic depressed patients (HAMD17), though a trend in the same direction was visible.

Conclusion

The results indicate that the two groups of chronically and nonchronically depressed individuals share a number of characteristics in the acute phase of depression. Symptom severity was similar and individuals in the two groups both experienced a significant symptom reduction in the course of their hospital stay. Simultaneously both groups significantly differed on a number of factors. The specificity of chronic depression was visible via the persevering and broad nature of the symptoms, ceasing at a slower rate while affecting all areas of life as was apparent in reduced psychosocial functioning, elevated rates of comorbidity as well as higher levels of neuroticism and lower levels of extraversion throughout the treatment process. These findings support the notion that both illnesses belong to the same disorder category – unipolar affective disorder – and that chronicity is a valid specifier for classifying individual unipolar affective disorders. The low extraversion scores in both groups highlight the need for measures to be sensitive to this very introverted target group and especially so for chronically depressed individuals. The elevated levels of neuroticism and reduced levels of extraversion in the group of chronically depressed individuals furthermore support the assumption of particular interpersonal difficulties experienced by this group of individuals. These interpersonal difficulties were also visible in the diagnoses of personality disorders with chronically depressed individuals being diagnosed more often with avoidant, negativistic, depressive as well as paranoid personality disorders.

Furthermore the study results indicate that individuals with chronic depression have experienced a greater number of adverse childhood events compared to nonchronically depressed individuals. It was interesting that group differences with respect to adverse childhood events were only found in the age category before the age of 6. This finding might stress the fragility of early childhood and its relevance for the development of affective disorders in the future. However the results have to be interpreted carefully since the differences were only significant in the univariate tests and were not included in the reduced model of the stepwise regression.

The results show the importance of differentiating between the two groups in the clinical context. Identifying individuals with chronic depression at the beginning of treatment is relevant for choosing and evaluating treatment options as well as for managing expectations of both doctors and patients since chronicity has a strong impact on the clinical course.

2 Zusammenfassung

Hintergrund

Eine chronische Form der Depression, die zwei Jahre oder länger andauert, erleben 20%-30% der von Depression betroffenen Menschen. (Arnow & Constantino, 2003; Lehmann, 1983; Gilmer et al., 2005; Wiersma, van Oppen, van Schaik, van der Does, Beekman, & Penninx, 2011). Chronische Depressionen stellen eine erhebliche, langanhaltende Belastung für Betroffene, ihre Familien sowie die Gesellschaft als Ganzes dar. Chronische Depressionen sind in den vergangenen Jahren in den Fokus der Forschung gerückt. Es ist jedoch weitere Forschung zu den Merkmalen von chronischer Depression zur Unterstützung frühzeitiger Diagnotik und adäquater Behandlung erforderlich.

Diese Arbeit hat zum Ziel, Erkenntnisse zu den differenzierenden Merkmalen chronischer Depression im Vergleich zu nicht-chronischer Depression zu gewinnen. Dabei liegt der Fokus auf klinischer Symptomatik, soziodemographischen Informationen, der klinischen und persönlichen Biographie, Persönlichkeitsfaktoren, psychiatrischer Komorbidität sowie Informationen zu stationärer Behandlung. Die drei begleitenden Hypothesen vergleichen chronisch und nicht-chronisch depressive Menschen in Bezug auf den erlebten Grad der Beeinträchtigung, neurotisch und extravertierte Persönlichkeitsstile sowie dem Ausmaß erlebter schwieriger Kindheitserlebnisse.

Methode

Die in dieser Arbeit analysierten Daten wurden im Rahmen einer Multi-Center Studie in einem prospektiven naturalistischen Setting gesammelt als Teil des Deutschen Forschungsnetzwerks zu Depressionen (Seemüller et al., 2009). Insgesamt nahmen 1073 Patienten an der Studie teil. In der aktuellen Arbeit wurden 954 Patienten mit unipolaren depressiven Störungen (ICD-10: F32, F33, F34) eingeschlossen und es wurden die Daten ausgewertet, die während des stationären Aufenthalts sowie zum follow-up Termin nach einem Jahr gesammelt wurden.

Chronische Depression wurde definiert als das Vorhandensein einer unipolaren affektiven Störung für mehr als zwei Jahre. Auf Basis dieser Definition wurden 113 Patienten (11,8%) als chronisch depressiv eingestuft.

Die Schwere der Depression wurde zweiwöchentlich mit den folgenden Instrumenten beurteilt: Hamilton Depression Rating Scale (HAMD) (Hamilton, 1967), Montgomery Asberg Rating Scale (MADRS) (Montgomery and Asberg, 1979), Beck-Depressions-Inventar (BDI) (Beck et al., 1961; Hautzinger et al., 1994). Persönlichkeitsmerkmale wurden bei Aufnahme und Entlassung mit dem NEO-Fünf-Faktoren-Inventar (Neo-FFI) (Costa, P.T. & McCrae, R.R., 1992) erhoben. Das individuelle Funktionsniveau wurde mit den folgenden Skalen erhoben: Global Assessment of Functioning Scale (GAF) (DSM-IV, American Psychiatric Association, 2000), Social and Occupational Functioning Assessment Scale (SOFAS) (DSM-IV, American Psychiatric Association, 2000), Clinical Global Impression rating scales (CGI) (Guy, 1976).

Soziodemographische, persönliche sowie klinische Informationen wurden mit der Basisdokumentation für klinische und soziodemographische Variablen in der Psychiatrie (BADO) (Cording et al., 1995) erhoben. Der exakte Test nach Fischer sowie T-Tests wurden angewandt zum Vergleich der Gruppen auf den oben beschriebenen Messgrößen. Um die relative Relevanz der Variablen einzuschätzen wurden logistische Regressionsanalysen berechnet. Anovas mit Messwiederholungen wurden durchgeführt um die Veränderung der klinischen und persönlichen Merkmale im Zeitverlauf zu analysieren.

Ergebnisse

Bei der stationären Aufnahme zeigten sich keine Unterschiede zwischen den Gruppen (chronisch vs. nichtchronisch depressiv erkrankte Menschen) in den via Fremdbeurteilung erhobenen Daten zu aktueller depressiver Symtomatik (HAMD 17, MADRS) sowie sozialem und beruflichen Funktionsniveau (GAF, SOFAS, CGI). Die Messwerte in beiden Gruppen deuteten auf hohe Beeinträchtigungen hin. Die beiden Gruppen unterschieden sich nur auf dem via Selbstbeobachtung erhobenen Fragebogen BDI sowie den Bereichen Neurotizismus und Extraversion auf dem NEO-FFI. Dabei erreichten chronisch depressive Menschen höhere BDI und Neurotizismus Werte sowie niedrigere Werte bei Extraversion.

Beide Gruppen profitierten stark von dem stationären Aufenthalt was sichtbar wurde in einer signifikanten Reduktion der Symptomatik auf allen Messgrößen (HAMD 17, MADRS, BDI, GAF, SOFAS, CGI) und positive Veränderungen in allen BIG FIVE Persönlichkeitsdimensionen (Neurotizismus, Extraversion, Offenheit für Erfahrungen, Verträglichkeit, Gewissenhaftigkeit).

Die Genesung in der Gruppe der chronisch depressive erkrankten Menschen war jedoch nicht so erfolgreich und bedurfte größerer Anstrengungen. Dies zeigte sich in längeren Krankenhausaufenthalten, einer größeren Bandbreite eingesetzter Medikamentenklassen, niedrigeren Remissionsraten, erhöhten Raten von Suizidgedanken sowie höheren Werten bei Messungen depressiver Smyptomatik (HAMD 17, MADRS, CGI) und niedrigeren Werte bei sozialem und beruflichen Funktionsniveau (GAF, SOFAS) bei Entlassung. Darüber hinaus zeigten eine Reihe von ANOVAs mit Messwiederholung signifikante Interaktionseffekte. Dies weist auf eine langsamere Veränderungsgeschwindigkeit der chronisch depressiv erkranken Menschen im Vergleich zu den nichtchronisch depressiv erkrankten Menschen hin (Daten zu Aufnahme und Entlassung: HAMD 17, MADRS, GAF, CGI; zweiwöchentlich erhobene Daten: MADRS). Zusätzlich wiesen chronsch depressiv erkrankte Menschen bei Entlassung weiterhin höhere Werte von Neurotizismus sowie niedrigere Werte von Extraversion im Vergleich zu nichtchronisch depressiv erkrankten Menschen auf. Bei dem Follow-up nach einem Jahr war die Depressivität der bei Aufnahme chronisch depressiv erkrankten Menschen im Vergleich zu nichtchronisch depressiv erkrankten Menschen nicht signifikant erhöht (HAMD 17), wobei ein Trend in diese Richtung erkennbar war.

Fazit

Die Ergebnisse weisen darauf hin, dass die zwei Gruppen chronisch und nicht chronisch depressiv erkrankter Menschen in der aktuten Phase der Depression eine Reihe von Merkmalen teilen. Der Schweregrad der Smyptomatik war vergleichbar und beide Gruppen erlebten eine signifikante Reduktion der Symptome im Verlauf ihres stationären Aufenthaltes. Gleichzeitig unterschieden sich beide Gruppen signifkant in Bezug auf eine Reihe von Faktoren. Die Besonderheit chronischer Depression war sichtbar im anhaltenden und umfassenden Charakter der Smptome welche langsamer weniger wurden während sie alle Bereiche des Lebens beeinträchtigten. Dies war erkennbar in dem reduzierten psychosozialen Funktionsniveau, erhöhten Komorbiditätsraten sowie einer höheren Ausprägung von Neurotizismus und niedrigeren Ausprägung von Extraversion während der Behandlung. Diese Erkenntnisse unterstützen den Ansatz, dass beide Erkrankungen zu der gleichen Störungs-Kategorie gehören – unipolare affektive Störungen – und dass Chronizität eine valide Spezifikation für die Klassifikation individueller unipolarer affektiver Störungen darstellt. Die niedrigen Werte von

Extraversion in beiden Gruppen heben die Notwendigkeit für die Sensitivität von Messinstrumenten für diese sehr introvertierte Zielgruppe hervor und hierbei insbesondere für chronisch depressiv erkrankte Menschen. Die erhöhten Werte von Neurotizismus und die niedrigen Werte von Extraversion in der Gruppe chronisch depressiv erkrankter Menschen unterstützen darüber hinaus die Vermutung besonderer zwischenmenschlicher Schwierigkeiten in dieser Gruppe von Menschen. Diese zwischenmenschlichen Schwierigkeiten werden auch sichtbar in der Diagnostik von Persönlichkeitsstörungen. Chronisch depressiv erkrankte Menschen erhielten häufiger die Diagnosen der vermeidenden, negativistischen, depressiven sowie paranoiden Persönlichkeitsstörung.

Darüber hinaus weisen die Ergebnisse daraufhin, dass Menschen mit chronischer Depression eine größere Anzahl adverser Kindheitserlebnisse erfahren haben im Vergleich zu nichtchronisch depressiv erkrankten Menschen. Interessant war dabei, dass die Gruppenunterschiede in Bezug auf adverse Kindheitserlebnisse nur für die Altersklasse unter 6 Jahren gefunden wurden. Dieses Ergebnis unterstreicht womöglich die Fragilität früher Kindheit und ihre Bedeutung in der späteren Entwicklung affektiver Störungen. Jedoch müssen die Ergebniss vorsichtig interpretiert werden da die Unterschiede nur in univariaten Tests signifikant waren und nicht im reduzierten Modell der schrittweisen Regression enthalten waren.

Die Ergebnisse zeigen die Relevanz der Differenzierung zwischen den beiden Gruppen im klinischen Kontext. Es ist für die Auswahl und Bewertung von Behandlungsoptionen sowie für den Umgang mit Erwartungen von Behandlern und Patienten wichtig, Menschen mit einer chronischen Depression zu Beginn der Behandlung zu identifizieren da Chronizität einen großen Einfluss auf den klinischen Verlauf hat.

3 Introduction

Chronic depression is a severe form of unipolar depression, which lasts two or more years (Klein, 2008a; McCullough, 2003). Around 20% - 30% of depressed individuals suffer from chronic depression (Arnow & Constantino, 2003; Lehmann, 1983; Gilmer et al., 2005; Wiersma et al., 2011). Chronic depression is strongly affecting the social, occupational and physical functioning of affected individuals over long periods of time with regular depressive treatments often not showing satisfying effects (Cuijpers et al., 2010; Gagné, Furman, Carpenter, & Price, 2000; Kocsis, 2003; McCullough, 2003). In the last decades, research on chronic depression has increased. Characteristics, course and effective treatment options for chronic depression have been explored (Negt, Brakemeier, Michalak, Winter, Bleich, & Kahl, 2016). However, the understanding of the development of chronic depression and its dynamics is still fragmented and incomplete. The distinctiveness of chronic depression compared to episodic depression has not yet clearly been grasped (Angst & Merikangas, 2001; Klein, 2008b; Uher, Payne, Pavlova, & Perlis, 2013). A number of clinical characteristics and factors related to chronic depression have been studied (systematic review: Hölzel, Härter, Reese, & Kriston, 2011; journal article: Wiersma et al., 2011). However, most characteristics did not show consistent results over a number of studies. In addition based on the varying definitions of chronic depression, many studies were based on small samples, focused on specific subgroups of chronic depression or on specific variables associated with chronic depression. These facts limit the explanatory power of the study results for the complete group of chronically depressed individuals. Only few studies have examainded a wider variety of varibles in a representative sample of depressed patientsnts. Therefore, more studies are required to build a sufficiently broad body of knowledge on this clinically relevant phenomenon of chronic depression.

This thesis aims to deepen the understanding of chronic depression. It hereby tries to add insights to the existing body of knowledge and to investigate the distinctiveness of chronic depression compared to nonchronic depression. The analysis comprises two steps. In a first step a crossectional analysis examines characteristics on which individuals with chronic depression possibly differ from individuals with nonchronic depression (depressive symptomatology, social and occupational functioning, clinical and personal history, personality patterns). The second step comprises a longitudinal analysis of the clinical course during a psychiatric inpatient stay and at

one-year follow-up. The thesis hereby compares the development of depressive symptomatology and psychosocial functioning of the chronically and nonchronically depressed individuals. Findings regarding similarities and differences between the two groups are thought to yield insights into the etiology, diagnosis, and treatment of this clinically burdensome phenomenon.

These research questions are being explored based on data collected from a large naturalistic inpatient sample with chronically depressed and nonchronically depressed individuals. Data collected in the study contain a number of clinical characteristics and factors possibly related to chronic depression such as age at onset, comorbid psychiatric illnesses, and critical life events experienced as a child, psychiatric family history as well as personality patterns. Furthermore, data include information regarding the course of depressive and psychosocial symptomatology during the inpatient stay and at the one-year follow-up.

Based on the systematic review of risk factors on chronic depression (Hölzel et al., 2011) the following three main hypotheses were compiled focusing on factors which have not been examined previously by a large number of studies. The three main hypotheses are introduced in the following paragraphs. The approach of further analyses was exploratory due to the naturalistic sample and the currently fragmented body of knowledge on the topic of chronic depression.

1) Level of impairment - Hypothesis

Chronically depressed individuals experience greater levels of impairment compared to nonchronically depressed individuals including higher levels of depressive symptom severity and suicidal ideation as well as lower levels of social and occupational functioning.

The impairment experienced by individuals with depression, in general, encompasses a wide spectrum beyond depressive symptoms. It includes severe social and occupational impairments in functioning as well as the burden frequently experienced by comorbid illnesses. The findings regarding chronic depression with respect to symptom severity, suicidal ideation, and functional impairments are mixed. Some study results indicate no differences between chronically and

nonchronically depressed individuals (Yang & Dunner, 2001, for individuals in the chronic major depression subgroup; Gilmer et al., 2005), some studies report lesser impairments for chronically depressed individuals (Yang & Dunner, 2001, for individuals in the dysthymic subgroup) and some found higher rates of impairment for chronically depressed individuals (Angst, Gamma, Rössler, Ajdacic, & Klein, 2009; Garvey, Tollefson, & Tuason, 1986; Klein, Taylor, Harding, & Dickstein, 1988b; Wiersma et al., 2011). Some of these mixed results might be influenced by subgroups of chronically depressed individuals making up different shares in each study group as apparent in the study by Yang and Dunner (2001) which found differing results for different subgroups of chronically depressed individuals (dysthymic vs. chronic major depression).

The study data in this study was collected in an inpatient setting. It was expected that the group of chronically depressed individuals experienced significant impairments justifying an inpatient stay. It was assumed that the impairment of this group of chronically depressed individuals was greater compared to nonchronically depressed individuals entailing different areas such as social and occupational functioning as well as suicidal ideation to a stronger degree compared to nonchronically depressed individuals.

2) Adverse Childhood Events – Hypothesis

Individuals with chronic depression have experienced a greater number of adverse childhood events compared to nonchronically depressed individuals.

`Adverse childhood events` is a term which comprises various critical and potentially traumatic events for children such as psychological, physical and sexual abuse as well as family conflicts and separations from family members. Findings comparing the occurrence of such events in chronically and nonchronically depressed individuals are mixed. A number of studies have found higher rates of adverse childhood events in the group of chronically depressed individuals (Angst, Gamma, Rössler, Ajdacic, & Klein, 2011; Wiersma et al., 2009; Lizardi, & Klein, 2000; Lizardi, Klein, Ouimette, Anderson, & Donaldson, 1995). The results of these studies, however, did not show a clear pattern – not all adverse childhood events were elevated in the group of chronically depressed individuals and the studies differed as to which events were reported more often in the

group of chronically depressed individuals. Furthermore, Yang and Dunner (2001) did not find any differences between chronically depressed individuals and nonchronically depressed individuals with respect to childhood adversity. Longitudinal studies underline the role of adverse childhood events for chronic depression showing a worse course with higher symptom severity and a greater number of depressive episodes for individuals with chronic depression who have experienced childhood adversity (Klein et al. 2009; Klein et al. 2008).

The data of this study included information on a number of critical life events (e.g. separation of parents). Based on the research findings the number of critical life events was expected to be higher in the group of chronically depressed individuals compared to nonchronically depressed individuals. The pattern of adverse childhood events which might be found to be higher in the group of chronically depressed individuals compared to nonchronically depressed individuals was planned to then be compared to the mix of patterns reported by earlier studies.

3) Neuroticism and Extraversion - Hypothesis

Individuals with chronic depression exhibit higher levels of neuroticism and lower levels of extraversion compared to individuals with nonchronic depression.

The results of a number of studies indicate that individuals with chronic depression exhibit at least temporarily accentuated personality styles compared to nonchronically depressed individuals and to normal controls (Wiersma et al., 2011; Robison, Shankman, & McFarland, 2009; Ormel, Oldehinkel, & Vollebergh, 2004; McCullough et al., 1994; Weissman, Prusoff, & Klerman, 1978). The domains of personality which appear to be concerned are neuroticism and the closely related construct of negative emotionality as well as extraversion and the closely related construct of positive emotionality. Individuals with chronic depression appear to portray higher levels of neuroticism and lower levels of extraversion compared to nonchronically depressed individuals as well as normal controls. However, not all studies reported differences on both domains and the strength of the effect varies widely. These variations might also be due to small sample sizes in many of the studies.

The analysis of the study data at hand with the large sample of patients aims to clarify the direction and strength of the relationship between personality domains and chronicity of depression. It is hypothesized that individuals with chronic depression exhibit higher levels of neuroticism and lower levels of extraversion compared to individuals with nonchronic depression. The course of the manifestation of personality styles over time will be analyzed following an explorative approach.

Following this brief introduction into the thesis the theoretical background is being described in greater detail in section 3 with a brief overview of the current status of understanding of chronic depression and details on the hypotheses introduced above. Subsequently, study methods and results are being reported in section 4 and 5, respectively. In the final section 6, key results of the study are being discussed.

4 Theoretical background

4.1 Definition and classification of chronic depression

4.1.1 Chronicity as a characteristic of unipolar affective disorders

Chronic depression is widely defined as an unipolar affective disorder which lasts two or more years without a period of two months or longer in which no symptoms occur (McCullough, 2003; Klein, 2008a). The two-year criterion is commonly applied even though Dunner (2005) has proposed to lower the threshold to one year.

This currently applied definition comprises a variety of unipolar affective disorder categories with different symptomatic patterns. These classifications are described in detail below for each of the currently relevant diagnostic manuals.

4.1.2 Chronic depression in the classification manuals (DSM-IV, DSM-V, ICD-10)

The currently valid diagnostic manuals in the field of psychiatric diagnoses are the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, & American Psychiatric Association (Eds.), 2013) and the tenth edition of the International Classification of Diseases and Related Health Problems (ICD-10) (World Health Organization (Ed.), 1992). The following section illustrates the diagnostic categories, which can apply to individuals with chronic depression. Since the recent revision of the DSM brought a major change for the diagnosis of chronic depression the preceding fourth edition of the DSM (American Psychiatric Association, & American Psychiatric Association (Eds.), 2000) will also be illustrated.

In the DSM-IV which has been replaced by the DSM-V in May 2013 the following categories could apply to individuals with chronic depression: dysthymic disorder, episode of a major depressive disorder (MDD) without full remission, chronic major depressive disorder (an episode of a major depressive disorder lasting longer than two years), concurrent diagnosis of a dysthymic disorder and a major depressive episode (also called double depression (Keller & Shapiro, 1982)) and a dysthymic disorder concurrent with a chronic major depressive disorder. The DSM-IV additionally offered a chronic specifier to document a chronic course of a

depression. The specifier was only descriptive and was not represented in a distinctive code. In addition, the proposed diagnostic category depressive personality disorder (DSM-IV, Appendix B) comprised some of the characteristic cognitive and behavioral patterns of individuals with chronic depression.

In the DSM-V, the conceptualization of chronicity has been altered. The DSM-V subsumes the formerly separate diagnostic categories dysthymia and chronic major depressive disorder under the category persistent depressive disorder (PDD). However, the diagnostic criteria for PDD correspond to the former criteria for dysthymia. They thereby exclude some of the characteristics of major depressive disorders such as loss of interest or pleasure, psychomotor retardation or agitation and accentuate other aspects such as low self-esteem instead of the worthlessness or guilt in the MDD criteria. In addition, the PDD diagnosis requires the existence of a depressed mood possibly disabling the tracking of individuals with a chronic depressive disorder without a depressed mood. Formerly these individuals could be diagnosed with MDD and the chronic specifier (chronic major depressive disorder). Since the specifier „chronic“ for MDD has been dropped the chronicity of these individuals cannot be displayed by a diagnostic category. Furthermore, the DSM-V does remain arbitrary in setting rules on how to diagnose individuals who fulfill both the criteria of MDD and PDD. They are not listed as exclusion criteria for each other. In section „Diagnostic features“ (pp. 169) it is noted that individuals who fulfill the diagnostic criteria of both categories should receive both diagnoses. In section „Differential diagnosis“ (pp. 170-171) it is noted that for individuals who fulfill the diagnostic criteria for MDD in the course of the two-year period the diagnosis PDD should be given with MDD noted as a specifier and not as a separate diagnosis (see Uher et al., 2013 for a detailed discussion). These classification issues might lead to possible ambiguities in the diagnosis of chronic depression and thereby to difficulties in the comparability of diagnoses and studies.

In the ICD-10, the classification is comparable to the DSM-IV. The difference lies in the fact that the ICD-10 does not explicitly state a chronic specifier, which would enable diagnostic personnel to explicitly document a chronic course. The problems related to the fact that chronicity cannot be documented in the ICD-10 is being discussed by Schnell et al. (2016). The article focuses on the difficulties of assessing personnel requirements for guideline-compliant and evidence-based inpatient treatment for individuals with chronic depression. In the ICD-10 individuals with

chronic depression might fulfill one of the following diagnostic categories: dysthymic disorder (F34.1), episode of a major depressive disorder lasting for more than two years (F32, F33), episode of a major depressive disorder without full remission lasting for more than two years (F32, F33), concurrent dysthymic disorder and an episode of a major depressive disorder (F34.1, F32, F33). Chronic depression in this thesis is defined based on these possible diagnostic constellations.

The conceptualizations and discussions described above portray the growing focus on chronicity as a decisive dimension of the depressive disorder. The varying categorizations also indicate that the current understanding of chronic depression has however not yet reached a mature state. Klein (2008a) and Klein and Kotov (2016), for example, have questioned the qualitative difference among the various diagnostic categories with respect to chronicity and have argued that chronicity and severity are the two main dimensions necessary in order to portray the heterogeneity of unipolar depression. The argument for an understanding of depression as a continuum rather than a discrete category is also supported by a study conducted by Angst and Merikangas (2001). They found that the validity of the depressive diagnoses could be enhanced by utilizing frequency and duration information in addition to the number of symptoms of depression.

Future diagnostic manuals, such as the ICD-11, which is currently up for revision and is expected to be published by the World Health Organization in 2018 will step by step incorporate more research findings and display the growing knowledge on chronic depression allowing them to grasp the phenomenon ever more precisely.

The current analysis of which the results will be reported below aims to hereby add insights into the distinct relevancy of chronicity as a descriptive characteristic of unipolar affective disorders. The term “chronic depression” will hereby refer to the definition described by McCullough (2003) and Klein (2008a) as an unipolar affective disorder which lasts two or more years without a period of two months or longer in which no symptoms occur. This definition is operationalised via the ICD-10 diagnostic constellations described above which fulfill the criterion of chronicity.

4.2 Demographic and clinical characteristics of chronic depression

4.2.1 Prevalence and symptomatology

Prevalence

The share of chronic depression is substantial. Approximately 20% - 30% of all depressed individuals develop a chronic depression (Arnow & Constantino, 2003; Gilmer et al., 2005; Gilmer et al., 2008; Lehmann, 1983; Wiersma et al., 2011). The symptoms of individuals with chronic depression comprise by definition the criteria of unipolar affective disorders as described in the ICD-10 or DSM-V, respectively. The severity and specific mix of symptoms varies in the course of a chronic depression. This variety is reflected in the respective disorder diagnoses appropriate at a given point in time. Since a large group of chronically depressed individuals exhibits the symptoms of a dysthymic disorder the hereby experienced severity of depressive symptoms tends to be lesser compared to individuals with a major depressive episode (see also Hölzel et al. 2011). However, characteristics specific for chronic depression have been found with respect to suicidal behaviors, which will along with other findings regarding symptomatology, be described below.

Depressive symptomatology

Yang and Dunner (2001) compared individuals with nonchronic major depression, chronic major depression (excluding double depression) and dysthymic disorder. With respect to symptomatology, they found similar HAMD and MADRS ratings for individuals with nonchronic and chronic major depression. The ratings for individuals with a dysthymic disorder were significantly lower. Their data showed no differences between the three groups with respect to a history of suicide attempts. Wiersma et al. (2011) compared chronically and nonchronically depressed individuals from a large naturalistic sample (n = 1002). They found a higher severity of depressive symptoms for chronically depressed individuals measured by the inventory of depressive symptomatology score. Klein et al. (1988b) found significantly higher rates of previous suicide attempts for individuals with double depression compared to individuals with episodic depression. They also reported higher rates of symptom severity on a self-report as well as on a clinician-rated measure for individuals with double depression compared to individuals with episodic depression. Garvey et al. (1986) also found chronically depressed individuals to

have significantly more often attempted a suicide in their life compared to nonchronically depressed individuals. They found no differences between the two groups with respect to symptom severity as measured by the clinician-rated Hamilton Depression score and Raskin Severity of Depression score as well as by the self-report Beck Depression score. Gilmer et al. (2005) did find no significant differences in HAMD17 scores between chronically depressed and nonchronically depressed individuals in a sample of 1380 outpatients. Angst et al. (2009) found chronically depressed individuals to report significantly more often thoughts of dying as measured by the SCL-90R. In a prospective study by Klein et al. (2008), they found that the characteristic "lifetime history of suicide attempts" did not predict the remission of chronic depression between the two waves of data collection (Wave 1: 2001-2002, Wave 2: 2004 -2005). Hölzel et al. (2011) observed in their systematic review of risk factors for chronic depression that the characteristic "more pronounced severity of the depression at discharge from inpatient treatment" has only been insufficiently examined currently.

Summing up the study results it can be stated that there is some evidence that chronically depressed individuals tend to report greater suicidal tendencies compared to nonchronically depressed individuals even though the results are not conclusive. With respect to symptom severity, the current state of research presents no clear picture. When developing hypotheses regarding an expected symptom pattern, the specific sample of the respective study, and hereby especially the share of dysthymic individuals and the share of individuals with a double depression, has to be taken into account. It can be hypothesized that in groups of chronically depressed individuals with a high share of individuals with a dysthymic disorder the depressive symptomatology might be less severe compared to groups of individuals with a nonchronic MDE or groups of chronically depressed individuals with a high share of individuals with an MDE lasting more than two years. Since all individuals in the sample of chronically depressed individuals displayed symptoms which were severe enough to justify hospital admission no large differences were expected between the group at admission with respect to depressive symptomatology. In this case, however, differences were expected between the groups at discharge with respect to both depressive symptomatology and suicidal ideation. It was hypothesized that the differences resulted from varying rates of change in the course of the inpatient stay and that they would remain up to the one-year follow-up. Overall it was suspected

that individuals with chronic depression were carrying a greater burden with respect to depressive symptomatology compared to nonchronically depressed individuals.

The following paragraph summarizes the main hypothesis regarding symptomatology:

1) Level of impairment - Hypothesis

Chronically depressed individuals experience greater levels of impairment compared to nonchronically depressed individuals on various dimensions including higher levels of depressive symptom severity and suicidal ideation.

In the study at hand, the differences between the two groups were expected to be especially pronounced at discharge from the hospital stay.

Further aspects of depressive symptomatology will be analyzed and reported with an explorative approach.

4.2.2 Comorbidity

The following paragraphs describe patterns and effects of comorbidity observed in chronically depressed individuals and nonchronically depressed individuals.

As mentioned above Yang and Dunner (2001) compared individuals with nonchronic major depression, chronic major depression (excluding double depression) and dysthymic disorder. Their data showed no differences between the groups with respect to panic disorder, eating disorder, alcohol or other substance abuse. Since the sample was drawn from a group of individuals, who had participated in pharmaceutical research studies the authors assumed that the sample might display less comorbidity than other samples.

There is evidence that comorbidity further impairs the outcome of chronic depression. Klein et al. (2008) for example found that a concurrent anxiety disorder significantly predicted a poorer 10-year outcome of the chronic depression. They analyzed data from individuals with either a dysthymic disorder or a double depression. Data were collected at baseline and 10 years later.

They found that among other predictors comorbid anxiety disorder to significantly predict HAMD scores at the 10-year follow-up date indicating that chronically depressed individuals with a comorbid anxiety disorder tend to have a worse outcome with respect to depressive symptomatology. In addition, they found the existence of a comorbid personality disorder to significantly predict a lesser change for the better over time. No influence was found for the existence of a substance abuse disorder.

Garcia-Toro et al. (2013) analyzed the course of chronic depression of a naturalistic sample at two waves (Wave 1: 2001-2002, Wave 2: 2004-2005). Individuals who did not experience a remission from their chronic depression during this period were significantly more often diagnosed with an axis I disorder at baseline, and hereby specifically more often with nicotine dependence, dysthymia, some form of an anxiety disorder and here specifically a generalized anxiety disorder.

As described above Wiersma et al. (2011) compared chronically and nonchronically depressed individuals. Chronically depressed individuals were significantly more likely to have been diagnosed with a comorbid anxiety disorder in the past year. In addition, they also reported a significantly larger number of medical illnesses.

Angst et al. (2009) analyzed data from the Zurich Cohort Study, a prospective study based on a community sample. They compared individuals with a chronic depression to individuals with nonchronic depression. Their data showed significantly higher rates of social phobia and benzodiazepine abuse for individuals with chronic depression. In addition, they found significantly higher treatment rates for generalized anxiety disorder, panic disorder, social phobia and benzodiazepine abuse.

Rhebergen et al. (2010) also reported higher rates of comorbid anxiety disorders for individuals with double depression compared to individuals with a nonchronic major depressive disorder.

In a study conducted by Klein et al. (1988b) the difference of comorbid rates of anxiety disorders for individuals with double depression compared to individuals with episodic depression was apparent but only marginally significant. They, however, found significantly elevated lifetime prevalence rates of eating disorders and severe personality disorders (borderline, antisocial,

schizotypal) for individuals with double depression compared to individuals with episodic depression. No difference was found for substance abuse between the two groups.

Riso et al. (2003) reported higher levels of personality disorders in the group of chronically depressed individuals compared to nonchronically depressed individuals. However, the differences were only significant on a general level and the groups did not differ significantly from each other when the clusters of personality disorders were tested separately.

In a systematic review, Hölzel et al. (2011) concluded that anxiety disorders and personality disorders were regularly found as comorbid disorders in chronically depressed patients. They judged the findings limited in their explanatory power with respect to a prognostic or etiological value due to the correlative nature of most results. They reported that furthermore elevated rates of substance abuse disorders were linked to individuals with chronic depression, a distinct relevant substance type could not be specified based on the current study results.

The findings described above highlight the relevance of comorbidity for the course of chronic depression. Especially anxiety disorders and related disorders – specifically benzodiazepine abuse – appear to co-occur frequently with chronic depression. The results also indicate elevated levels of personality disorders even though the specific pattern appears less clear. The findings, however, do not address the question of causation as was also pointed out by Hölzel et al. (2011). It can be hypothesized that in some cases chronic comorbid illnesses might foster the development of a chronic depression. It can simultaneously be speculated that in some cases chronic depression might raise the vulnerability or at least impair the healing process of a later developed comorbid illness.

The current study analyzes comorbid psychiatric disorders in a sample of chronically and nonchronically depressed individuals whose symptom severity justifies an admission for inpatient treatment. It is assumed that the sample of the current study will exhibit a comorbid pattern similar to the patterns described above with elevated levels of comorbid anxiety disorders and higher rates of benzodiazepine abuse as well as personality disorders in the group of chronically depressed individuals compared to nonchronically depressed individuals.

The comorbid pattern found in the two groups of chronically and nonchronically depressed individuals will be analyzed and reported following an explorative approach.

4.2.3 Treatment

Chronic depression is by definition an illness, which does not easily respond to general treatment approaches applied in the field of unipolar affective disorders leading to the defining chronic course. Therapeutic approaches that have been shown effective in the treatment of depression such as Cognitive Behavioral Therapy for Depression (CBT-D) (Beck et al., 1979) and Interpersonal Therapy (IPT) (Klerman et al. 1984) have failed to replicate their efficacy in the context of chronic depression (McCullough, 2003; Cuijpers et al., 2010). Antidepressant medication has been shown to be effective in the treatment of chronic depression (Kocsis, 2003; de Lima et al., 1999). However, it does currently not result in sufficiently satisfying remission rates (Kocsis, 2003) and in preventing relapses reliably (Gagné et al., 2000).

Within the last decades the focus on chronic depression has increased and McCullough (2003) has proposed a specific treatment program for patients with chronic depression, the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) which has been shown to be effective in the treatment of this group of patients (Keller et al., 2000). In his study, Keller et al. (2000) demonstrated similar treatment effects for treatment with nefazodone and treatment with CBASP in groups of chronically depressed individuals. The best treatment results were achieved with a treatment, which combined the pharmaceutical (nefazodone), and psychotherapeutic (CBASP) approaches. In a further study, Keller et al. (1998) found satisfying treatment results for chronically depressed individuals when treated with either sertraline or imipramine. In a small study, Swan et al. (2014) found CBASP to be an effective treatment method for chronically depressed individuals (n (completers) = 46). In their study, 60% of individuals who completed the CBASP treatment experienced clinically significant improvements. Schramm et al. (2015) also reported CBASP to be comparably effective to treatment with Escitalopram resulting in high response rate and moderate remission rates among the chronically depressed individuals treated in the two outpatient groups. Compared to nonspecific psychotherapy CBASP appeared to be moderately more effective in an outpatient population without antidepressant medication (Schramm et al., 2017). A study conducted by Brakemeier et al. (2015) showed promising results implementing the CBASP approach in a 12-week inpatient setting. CBASP has also been shown to be effective in combination with Mindfulness-Based Cognitive Therapy (MBCT) with a focus on treating suicidal ideation (Forkmann et al., 2016). MBCT, however, does appear to be less

effective than CBASP when applied in combination with treatment as usual (Michalak et al., 2015).

Behavioral activation therapy with the goal of returning to work was tried out in a pilot study adressing individuals who responded to initial medication treatment but who had not yet regained their work functioning (Hellerstein et al., 2015). The results of this small study were encouraging showing improvements on work related activity, paid work, and productivity as well as on earned income at the 24-week follow-up.

Further possible treatment approaches, which are applied for chronic depression in clinical settings, encompass transcranial magnetic stimulation (TMS) and electroconvulsive shock treatment (ECT). To the knowledge of the author, so far only studies with small sample sizes have reported experiences with TMS (e.g. Vanneste, Ost, Langguth, & De Ridder, 2014; Januel et al., 2004) for individuals with chronic depression. Kellner et al. (2014) report in their review that ECT is mainly used as a treatment for severe and treatment-resistant depressions and is therefore applied in the area of chronic depression. Dombrovski, Mulsant, Haskett, Prudic, Begley, and Sackeim (2005) found chronicity to be a predictive factor for the success of ECT with chronically depressed individuals having lesser chances of remission compared to nonchronically depressed individuals when being treated with ECT. Gagné et al. (2000) reported positive effects of ECT not only as an acute treatment but also as a relapse prevention for individuals with chronic depression in combination with continued antidepressant medication.

In a meta-analysis, Cuijpers et al. (2010) confirmed the appraisal of Keller et al. (2000) that a combined treatment – psychotherapy and pharmacotherapy – produces the best results. Their analyses also indicate that psychotherapy alone is effective however not as effective as pharmacotherapy, especially with SSRIs (selective serotonin reuptake inhibitor), alone. A recent meta-analysis of randomized-controlled clinical trials of CBASP conducted by Negt et al. (2016) found positive effects of CBASP compared to treatment as usual as well as interpersonal therapy and similar effects compared to antidepressant medication. It furthermore reported superior results for a combination treatment of CBASP with antidepressant medication compared to antidepressant medication alone. These findings are also reflected in the recommendations on psychotherapy for chronic depression compiled by the European Psychiatric Association (Jobst et al., 2016).

The current study was not originally conducted with a specific focus on chronically depressed individuals. It was a naturalistic inpatient study and patients were treated at the discretion of their mental health experts. Therefore, no standardized treatment regimen was defined and the results are not suitable to make statements with respect to certain treatment methods. However, the treatment methods applied will be described. This description can be used as a general overview of the treatments applied in naturalistic inpatient settings.

4.2.4 Family history and biological factors

A number of studies, which have been conducted with various subgroups of chronic depression, have shown interfamilial accumulations of affective disorders as described below.

Klein, Shankman, Lewinsohn, Rohde, and Seeley (2004) compared family histories of individuals with a dysthymic disorder, chronic major depression, episodic major depression and no depressive disorder. Their data showed that individuals with either a dysthymic disorder or a chronic major depression had a significantly higher rate of first-degree relatives with a major depressive disorder. In addition, they found that first-degree relatives of individuals with a dysthymic disorder had significantly higher rates of dysthymic disorders compared to individuals with no depressive disorder and that first-degree relatives of individuals with chronic major depression had significantly higher rates of chronic major depression compared to individuals with no depressive disorder.

Lizardi et al. (2000) analyzed the family history of a sample of individuals with a dysthymic disorder, an episodic major depression or no psychiatric illness with respect to mood and personality disorders. Their data showed that mothers of individuals with a dysthymic disorder had higher rates of mood disorders as well as personality disorders compared to mothers of individuals with no depressive disorder. Fathers of individuals with a dysthymic disorder also had significantly higher rates of personality disorders compared to fathers of individuals with no depressive disorder. Mothers of individuals with a dysthymic disorder had higher rates of mood disorders and fathers of individuals with a dysthymic disorder had higher rates of personality

disorders compared to the respective parents of individuals with an episodic major depressive episode.

Klein et al. (1988b) reported higher rates of bipolar I and nonbipolar depressive disorders in first-degree relatives of individuals with double depression compared to individuals with episodic major depression. Additionally, there were a higher number of individuals with double depression with both parents suffering from affective disorders compared to individuals with episodic major depression.

Garvey et al. (1986) however found no differences between chronically depressed individuals and nonchronically depressed individuals with respect to the rates of neither depressed, manic nor alcohol-related disorders in first-degree relatives. Yang and Dunner (2001) reported similar results. They also found no significant differences between rates of depression, bipolar disorders or substance abuse disorders in first-degree relatives of nonchronically depressed, chronically depressed and individuals with a dysthymic disorder.

Hölzel et al. (2011) concluded in their systematic review on risk factors for chronic depression a family history of mood disorders to be a consistently found risk factor for the development of chronic depression. For the factor family history of substance abuse, they judged the study results to be inconsistent. Furthermore, they stated that the research on biological risk factors for chronic depression was not sufficient for conclusions to be drawn.

The results delineated above indicate that the presence of an affective disorder presents a risk factor for the development of an affective disorder and specifically for the development of a chronic depression. The pathway, which the risk factor takes, has not yet been conclusively clarified. It can be hypothesized that both biological as well as environmental aspects and their interaction are involved in the development of the relationship between a family history of mood disorders and the development of a mood disorder in the next generation.

The current study assessed the family history of psychiatric disorders of first-degree relatives. The data on the individual family history found in the two groups of chronically and nonchronically depressed individuals will be analyzed and reported following an explorative approach.

4.2.5 Personal history and childhood adversity

Childhood adversity comprises a number of very different and at the same time often highly intercorrelated aspects such as critical lifetime events (e.g. the death of a parent), family conflicts (e.g. separation of parents), difficult interpersonal and educational situations (e.g. emotional neglect) as well as psychological, physical and sexual abuse experienced or witnessed by the child. A number of studies have investigated the association between childhood adversity and chronic depression.

Wiersma et al. (2009) found childhood trauma to be linked to chronic depression. Childhood trauma was assessed based on the Childhood Trauma Interview (Fink, Bernstein, Handelsman, Foote, & Lovejoy, 1995) focusing on four aspects: emotional neglect, psychological abuse, physical abuse, and sexual abuse. Childhood life events (parental loss, divorce of parents, and separation from home) were not associated with chronicity.

Negele et al. (2015) also found childhood trauma to be related to chronic depression. Within the group of chronically depressed individuals, 76% reported having experienced some kind of childhood trauma in their life. Thereof, 37% experienced multiple childhood trauma. Their analysis indicated a relationship between sexual and emotional abuse and the number of current depressive symptoms. Furthermore, multiple exposures to childhood trauma appeared to be a significant predictor of symptom severity in chronically depressed individuals.

Lizardi et al. (1995) demonstrated in a study that individuals with early-onset dysthymia reported worse relations with both parents compared to individuals with episodic major depression. They also reported more physical as well as sexual abuse compared to normal controls (The difference to individuals with episodic major depression was not significant). No difference was found for parental loss among the groups.

As described above individuals with chronic depression often have a positive family history with other psychiatric illnesses. These illnesses might be in part responsible for the experience of childhood adversity through the effects psychiatric illnesses have von parenting styles. Lizardi et al. (2000) however found evidence in a further study that even when controlling for parental psychopathology (mood and personality disorders) the quality of maternal relationships, maternal

as well as paternal care were less for individuals with dysthymia compared to individuals with episodic major depression. When compared to normal controls and with parental psychopathology controlled for, individuals with dysthymia reported higher rates of physical abuse, a worse quality of maternal and paternal relationships, less maternal and paternal care and more maternal and paternal overprotection.

The study Yang and Dunner (2001) conducted, however, showed no difference between individuals with dysthymic disorders, chronic major depression or non-chronic major depression with respect to a history of sexual abuse or history of physical abuse.

In an analysis of data from a representative sample, Angst et al. (2011) found that childhood family problems significantly increased the risk of chronicity. Family problems entailed the following aspects: tense family atmosphere, broken home, problems within the family, mother or father with psychological problems, conflicts with or between parents or with other persons, more punished than peers and disliked, rejected by peers. Conduct problems (trouble with the police, unpunctual, frequent physical fights, discipline problems at school, repeated running away, theft, and truancy), as well as sexual trauma were not found to be associated with chronicity.

There is also evidence for the relevance of parental relationships and childhood adversity with respect to the long-term course of chronic depression. A trajectory long-term study by Klein et al. (2008) showed a worse 10-year course of chronic depression for individuals with a poorer maternal relationship and a history of sexual abuse in the childhood.

The results reported above demonstrate that there is a large heterogeneity in the definition and exploration of childhood adversity rendering it difficult to conclusively evaluate the relationship between childhood adversity and chronic depression. The data indicate that the two phenomena are not completely independent, the question on how and which aspects of childhood adversity affect the development of a chronic depression is not yet sufficiently answered. A study conducted by Klein et al. (2009) however indicates that individuals who have experienced childhood adversity and who have subsequently developed a chronic depression are suffering more intensely with an earlier onset, greater symptom severity, a greater number of episodes, a

longer duration of the disease, elevated suicidality, more comorbid diagnoses as well as greater functional impairment (Klein et al. 2009).

For the current study we therefore expect elevated levels of adverse childhood events in the group of chronically depressed individuals compared to nonchronically depressed individuals.

2) Adverse Childhood Events – Hypothesis

Individuals with chronic depression have experienced a greater number of adverse childhood events compared to nonchronically depressed individuals.

4.2.6 Personality characteristics

A number of studies have shown evidence that individuals with chronic depression differ from individuals with nonchronic depression as well as from healthy controls with respect to their personality style. Differences which were each replicated in several studies show that within the personality domains of the Big Five (Goldberg, 1981; Goldberg, 1982; historic overview in Franić, Borsboom, Dolan, & Boomsma, 2014) individuals with chronic depression exhibit lower levels of extraversion and greater levels of neuroticism compared to normal controls or individuals with nonchronic major depression (Wiersma et al., 2011; Weissman, Prusoff, & Klerman, 1978; McCullough et al., 1994; Ormel et al., 2004). Extraversion hereby refers to an elevated orientation towards participation in social interaction and an energetic attitude. Neuroticism refers to the tendency to be sensible towards negative emotions such as anxiety, depression or anger indicating a reduced level of emotional stability. However, not all studies found both domains to differ for individuals with chronic depression as will be described below in greater detail.

Studies also reported lower levels of Positive Emotionality (PE) and higher degrees of Negative Emotionality (NE) for individuals with chronic depression compared to individuals with nonchronic depression (Robison et al., 2009). Positive emotionality and negative emotionality are closely related to the terms Positive Temperament and Negative Temperament (Watson & Clark, 1995). Positive emotionality refers to the ability or tendency to experience positive emotions such

as joy, enthusiasm, and energy. Negative emotionality refers to the extent to which a person experiences unpleasant emotions such as fear, depressed moods or anger. PE and NE are linked to the constructs of extraversion and neuroticism as part of the Big Five. Extraversion has been found to be highly correlated with PE and neuroticism has been found to be highly correlated with NE (Robison et al., 2009).

The results of various multiple regressions by Robison et al. (2009) pointed to a relationship between both PE and NE and chronicity of depression. Hereby the relationship between PE and chronicity appeared to be stronger. The results of one logistic regression by Robison et al. (2009) showed that only positive emotionality and not negative emotionality predicted chronicity of depression when depression severity was controlled for. A reversed logistic regression yielded the result that chronicity explicitly predicted positive emotionality and not negative emotionality. Overall, in the follow-up after 6 months, the level of negative emotionality was reduced and the level of positive emotionality was elevated along with a decrease in symptom severity for both groups. They also found that in the six-month follow-up, individuals with chronic depression still reported significantly higher degrees of negative emotionality, the differences in positive emotionality were not significant anymore. However, in the multiple regression using average values for personality traits and depression severity (baseline, six-month follow-up) they found that positive as well as negative emotionality each uniquely predicted chronicity whereas chronicity only significantly predicted positive emotionality.

The result of a study by Wiersma et al. (2011) showed elevated levels of neuroticism and lower levels of extraversion, agreeableness as well as conscientiousness for individuals with chronic depression compared to individuals with nonchronic depression. However, when tested with multivariate methods, they found that only a low degree of extraversion showed increased odds for chronic depression.

Hirschfeld, Klerman, Andreasen, Clayton, & Keller (1986) as well as Weissman et al. (1978) found neuroticism to predict a chronically depressive course within their study samples. Extraversion was not significantly linked to a chronic course. Weissman et al. (1978) hereby reported the results that patients with a chronic course had higher neuroticism scores at baseline, 8, 20 and 48 months after an acute episode of depression compared to patients with an asymptomatic or moderate course. No difference was found between the groups in the domain of

extraversion. These results are in line with the analyses by McCullough et al. (1994) who only found neuroticism and not introversion scores in a sample of individuals with dysthymia (with and without superimposed major depressive episodes) to be elevated compared to healthy controls.

Scott, Barker, & Eccleston (1988) however found no significant differences for chronically depressed individuals compared to nonchronically depressed individuals neither for the domain neuroticism nor for the domain extraversion.

With regard to the course of personality styles and the influence of depressive symptomatology Ormel et al. (2004) found evidence in an analysis that depressive symptomatology influences the scores while the symptoms are present. They, however, observed no long-term negative change (scar effect) of depressive symptomatology on personality traits. Their results showed higher premorbid vulnerability scores on all personality measures including neuroticism for individuals who later developed a major depressive episode (MDE). During the MDE, individuals showed even more elevated vulnerability scores. After remission of the MDE, the vulnerability scores subsided and returned to premorbid levels. These results were similar for first time MDE and recurrent MDE. The findings bear an interesting finding concerning the relevance of personality styles. Since premorbid levels of personality styles were elevated towards a pathological direction for individuals who later developed depressive symptoms it can be hypothesized that these personality styles and the associated cognitive patterns have played a role in the development of the depressive pathology. Their analyses, however, did not comprise individuals with chronic depression so the validity for this specific group is limited.

A study by Duggan, Lee, and Murray (1990) showed a predictive power of neuroticism scores but not for extraversion. The assessment of personality traits was measured during a depressive episode. In a follow-up conducted 18 years later, individuals who had had higher levels of neuroticism at baseline showed a worse global outcome indicating a relevant interaction of personality pattern and depressive pathology.

An analysis conducted by Hirschfeld (1990) showed that the personality pattern of individuals with a dysthymic disorder who had in an earlier analysis (Klein et al., 1988a) revealed higher

levels of stress reactivity (comparable to neuroticism) and lower levels of extraversion, remained the same after their recovery from dysthymia.

The results of the studies described above indicate that individuals with chronic depression tend to exhibit a more pathological personality style compared to nonchronically depressed individuals and normal controls. There is also evidence supporting the hypothesis that the difference between the groups exists independent of depressive symptomatology. It is hereby presumed that an acute depressive episode temporarily accentuates the scores towards a pathological direction for all groups and that the scores are moving back to lower premorbid levels once symptom severity subsides. However, across the studies the reported pattern is not completely consistent with some studies showing uniquely a significant predictive power for neuroticism or negative emotionality while others show only a significant predictive power for extraversion or positive emotionality and further results indicating a predictive power for both or none. In addition, a number of studies employed only a small sample limiting the explanatory power for the question at hand. To the knowledge of the author, there exists up to this point no meta-analysis, which integrates the current body of knowledge on the relationship between personality styles and chronicity of depression.

The study results, which are reported in this thesis, comprise a large sample of patients and will be used to further clarify the specific direction and strength, as well as the course of personality styles, during an inpatient stay in the group of chronically depressed individuals compared to nonchronically depressed individuals. It is hypothesized that the groups of chronically and nonchronically depressed individuals differ with respect to the displayed levels of neuroticism as well as extraversion both at admission and at discharge. It is furthermore assumed that in both groups a change will take place during the inpatient stay in the form of a reduction of neuroticism levels and a rise of extraversion levels.

3) Neuroticism and Extraversion - Hypothesis

Individuals with chronic depression exhibit higher levels of neuroticism and lower levels of extraversion compared to individuals with nonchronic depression.

Further personality aspects will be analyzed and reported following an explorative approach.

4.3 Course of chronic depression

4.3.1 Onset

It has been shown in a variety of studies that individuals with chronic depression experience their first depressive symptoms and first depressive episodes at an earlier age compared to individuals with nonchronic depression (Garcia-Toro, 2013; Klein et al., 1988a; Garvey et al., 1986). Not all studies were able to replicate a significant difference between the groups with respect to the onset of depression.

Garcia-Toro et al. (2013) showed that individuals with chronic depression did not only report an earlier age at onset but also a relatively later age at first treatment – treatment delay – compared to individuals with nonchronic depression. In addition, as to be expected, individuals with chronic depression reported a significantly longer duration of their longest episode.

The data analyzed by Wiersma et al. (2011) however showed no significant difference between individuals with chronic depression and individuals with nonchronic depression with respect to the onset of depression. Early onset of depression was hereby defined with 21 years or younger and a categorical comparison between the two groups was carried out. The share of individuals with chronic depression who reported an early onset of depression was not significantly higher compared to the share of individuals with nonchronic depression who reported an early onset of depression.

Yang and Dunner (2001) found no significant differences between individuals with nonchronic major depression, individuals with chronic major depression and individuals with a dysthymic disorder. Chronic major depression was hereby defined as a major depressive episode with a duration of more than two years excluding individuals with a superimposed dysthymic disorder. The mean values showed a tendency that individuals with a dysthymic disorder had a slightly lower mean age of onset compared to individuals with chronic depression or individuals with nonchronic depression.

Klein et al. (1988b) compared individuals with double depression to individuals with episodic major depression. They also found no significant differences between the groups. However, the

sample was small (n = 81) and the mean values showed a trend that individuals with double depression had experienced a slightly earlier onset of their depression.

Ramklint and Ekselius (2003) analyzed the characteristic “early onset of depression” in a sample of 400 depressed primary care patients. Early onset depression was defined as a depression with an initial onset at the age of 25 or younger (Parker, Wilhelm, Mitchell, Austin, Roussos, & Gladstone, 1999). Ramklint and Ekselius found in their sample that individuals with an early onset of depression reported a worse course of their depression expressed through more depressive episodes and more previous hospitalizations. Their findings stress the relevance of the characteristic “early onset of depression” and indicate that apart from being a risk factor for the development of a chronic depression, an early start of depressive symptomatology poses a general risk factor for a more difficult course of a depressive disorder.

An analysis by Klein et al. (1999b) additionally demonstrated the relevancy of the age at onset of depression. They compared two groups of individuals all of who had dysthymic disorders and superimposed major depressive episodes whereby one group reported an early onset (< age 21) and the other group a late onset (≥ age 21). They found that individuals with an early onset experienced a significantly longer index episode of major depression indicating that individuals with an early onset are affected stronger by depressive episodes.

As described above there is evidence indicating that individuals with chronic depression experience their first depressive episode at an earlier age. A systematic review by Hölzel et al. (2011) judged a younger age at onset to be one of only three consistent risk factors among the large number of studies included in their review. However as shown above even for this risk factor the evidence is not completely without ambiguities with a study with a large naturalistic sample showing no differences among the groups (Wiersma et al., 2011). Therefore, the results of this study aim to further clarify the role of the age at onset of depressive symptomatology for the development of a chronic depression. The current analysis also takes into account the treatment latency after the onset of depressive symptomatology. Here it is assumed that the treatment latency for chronically depressed individuals is longer possibly intensifying the depressive symptoms.

The characteristics ‘age at onset’ and ‘treatment latency’ are analyzed and reported following an explorative approach.

4.3.2 Long-term development and Psychosocial Functioning

All forms of depression have been shown to significantly impair the quality of life as well as the psychosocial functioning of the individuals affected by it (Ustün, Ayuso-Mateos, Chatterji, Mathers, & Murray, 2004; Wittchen et al., 2011). Chronic depression, by definition, is a form of depression with a long duration thereby amplifying the exerted burden over long periods in the lives of the affected individuals. In addition, research indicates that the projection for individuals with a diagnosed chronic depression is significantly worse compared to individuals with nonchronic depression (e.g. Wells, Burnam, Rogers, Hays, & Camp, 1992). Within the group of chronically depressed individuals there appear to be additional variables moderating the long-term course of the depression. For example, Klein et al. (2008) were able to identify demographic, clinical, family history, and early adversity variables affecting the severity of the depressive course. Their sample consisted of 87 individuals with early-onset chronic depression (< 21 years). A longer duration of the dysthymic disorder was linked to a greater functional impairment at the 10-year follow-up.

In addition to the longer duration of the periods with depressive symptoms compared to other affective mood disorders, individuals with chronic depression experience greater numbers of comorbid disorders as shown above (see section 3.2.2. Comorbidity). These factors may be in part responsible for the greater psychological and occupational impairments found for individuals with chronic depression.

Leader and Klein (1996) for example found that all observed groups (individuals with only a dysthymic disorder, a double depression or a major depressive episode) were found to have a significantly lower social as well as occupational functioning compared to normal controls. The group of individuals with a double depression experienced an even lesser degree of functioning compared to individuals with a dysthymic disorder or individuals with a current major depressive episode indicating that both severity and chronicity are relevant independent factors affecting

human functioning. The impairment reported by individuals with a dysthymic disorder, which is defined as an affective disorder with a reduced symptom severity compared to a major depressive episode, was comparable to that reported by individuals with a current major depressive episode. These results indicate that the chronically present symptoms produce severe functional impairments that are equivalent to the impairments experienced during major depressive episodes.

Rhebergen et al. (2010) reported similar results. They also found chronically depressed individuals – both with only a dysthymic disorder or with a double depression – and nonchronically depressed patients to experience a significantly higher degree of social and physical impairment in functioning compared to healthy controls as measured with the Groningen Social Disability Schedule and the SF-36 physical health summary scale. After recovery from the respective disorders, the formerly chronically depressed individuals demonstrated a lower post-morbid level of functioning compared to the individuals who formerly suffered a major depressive episode. These results indicate that the significant functional impairment experienced during a chronic depression does not disappear along with the fading of depressive symptoms but tends to persist even after the remittance of depressive symptoms. This development involves prolonged suffering and presumably raises the vulnerability for a recurrence of a depressive disorder.

Agosti (2014) showed that individuals who were in remission from a chronic depression still experienced worse psychosocial as well as physical functioning compared to a community sample measured by Short-Form health scores.

As mentioned above Yang and Dunner (2001) compared individuals with nonchronic major depression, chronic major depression (excluding double depression) and dysthymic disorder. The GASF scores revealed a significantly lower degree of functioning for individuals with a dysthymic disorder compared to individuals with an either nonchronic or chronic major depression.

Generally, it can, fortunately, be stated that most individuals recover from depressive disorders including chronic depression. Mueller et al. (1996) demonstrated for example that after a 10-year period 93% of the total sample of 431 individuals had recovered from their major depressive

episode they were diagnosed with at baseline. In addition, out of the 35 individuals who had not recovered within the first five years (chronically depressed), another 38 % recovered in the course of the following five years.

These findings show that recovery can take place also after long periods of a diagnosed depression. They however also provide an estimate with respect to the duration of the associated impairment. In a naturalistic outpatient sample Garcia-Toro et al. (2013) found that of the 504 individuals who fulfilled the criteria for a chronic major depressive disorder at wave 1 (2001-2002), only 63 (11.53%) fulfilled the criteria for a chronic major depressive disorder at wave 2 (2004-2005). Their data also indicated a causal relationship between experienced individual functional impairment and remittance of the chronic major depressive disorder. Individuals with a persistent chronic major depressive disorder at wave 2 had on average experienced worse psychosocial functional impairments as measured by the SF-12 physical component summary, social function scale, mental health component, and role emotional component scales.

The current study aims to replicate the results on social and occupational functioning. Due to the inpatient setting it is expected that at intake both groups (chronically and nonchronically depressed individuals) experience severe functional impairments. It is furthermore expected that as the depression severity subsides due to the intensive inpatient treatment individuals with only a major depressive episode display a higher degree of functioning compared to the group of chronically depressed individuals at discharge.

These assumptions are subsumed within the hypothesis which has already been introduced earlier referring to the greater levels of impairment experienced by chronically depressed individuals compared to nonchronically depressed individuals.

1) Level of impairment - Hypothesis

Chronically depressed individuals experience greater levels of impairment compared to nonchronically depressed individuals on various dimensions including social and occupational functioning.

4.3.3 Health care utilization

In addition to the burden depressive symptoms pose on chronically depressed individuals for long stretches of time and the accompanied functional impairment – both described above – chronic depression has been found to be associated with a high level of health care utilization. The utilization is presumably linked on the one hand to the long periods of illness, which are by definition a part of chronic depression as well as to the currently not completely satisfying treatment results described below. The high utilization of health care offerings poses a large financial burden on the affected individuals and their families as well as on society as a whole.

In their review, Arnow and Constantino (2003) describe depression to be the illness, which is associated with most missed days at work compared to other psychiatric and non-psychiatric illnesses. They also report depression to have been the fourth most costly illness in 1990. In addition, they describe evidence that individuals with chronic depression have higher rates of hospitalizations as well as high rates of medical use.

The study by Garcia-Toro et al. (2013) also showed higher levels of health care utilization as a sign of a worse course of a chronic depression. Individuals with chronic depression who did not show remittance at wave 2 (2004-2005, wave 1: 2001-2002) reported higher rates of lifetime treatment seeking.

Yang and Dunner (2001) found that individuals with a major depressive episode that lasted for longer than two years (11.5%) had been previously hospitalized in a psychiatric setting significantly more often compared to individuals with a major depressive episode that had lasted for less than two years (7.6%) or individuals with a dysthymic disorder (1.1%). Villoro, Merino, & Hidalgo-Vega (2016) also found individuals with chronic depression to have stayed longer in hospitals and utilized emergency services more often.

Hölzel et al. (2011) conclude in their systematic review on risk factors for chronic depression that there is not yet enough research as to make statements concerning differences in inpatient stays as well as to the employment status of chronically versus nonchronically depressed individuals.

The sample of this study is made up of individuals who were admitted to a psychiatric hospital based on their affective disorder. It is therefore presumably a subgroup of depressed individuals

with a severe course either with respect to symptom severity or with respect to chronicity requiring extensive medical care. With the data, the aim was to analyze two aspects of healthcare utilization - number of past stays in psychiatric hospitals and the duration of the current hospital stay. Based on the current research it was assumed that individuals with chronic depression have experienced a greater number of past psychiatric hospitalizations and require more days of inpatient stay before being discharged. These two aspects – the number of past stays in psychiatric hospitals and the duration of the current hospital stay – might underline the overarching hypothesis introduced above regarding the impairment experienced by individuals with chronic depression.

1) Level of impairment - Hypothesis

Chronically depressed individuals experience greater levels of impairment compared to nonchronically depressed individuals on various dimensions including social and occupational functioning.

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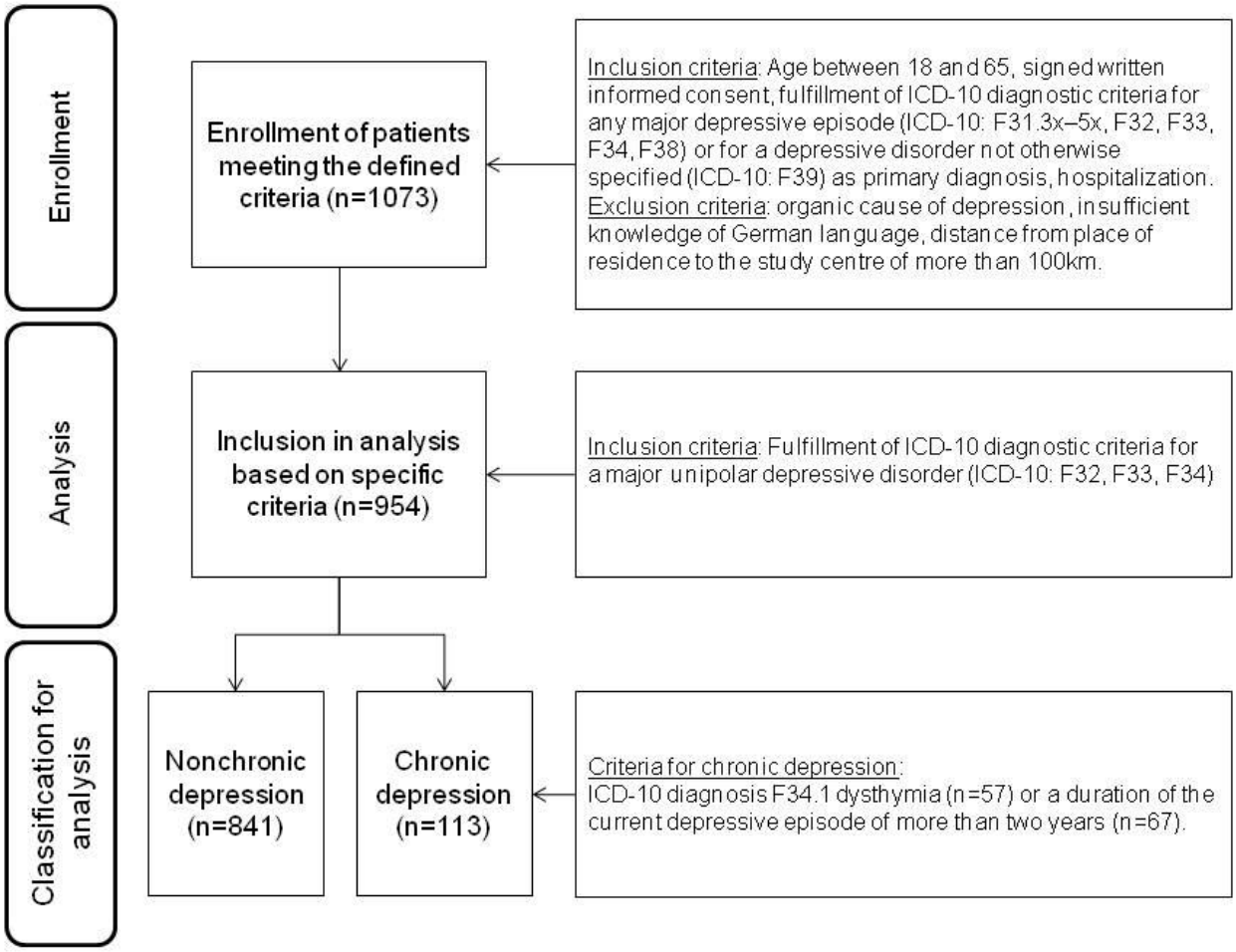
5 Method

5.1 Sample

The data analyzed in the present study were collected within the scope of a multicenter trial conducted as part of the German research network on depression. The prospective naturalistic study was designed to gain insights on treatment resistance, relapse, chronicity, and suicidality in depressive disorders. The study took place at psychiatric university and district hospitals across Germany (university hospitals: Berlin: Campus Charité Mitte and Campus Benjamin Franklin, Düsseldorf, Halle, Heidelberg, Munich: MPI and LMU; district hospitals: Gabersee/Bavaria, Haar/Bavaria, Berlin: Auguste-Viktoria-Hospital, St Joseph hospital and St Hedwig hospital). Clinical research coordinators supported protocol implementation and data collection at each location. The study was funded by the German Federal Ministry of Education and Research (BMBF). Participants were between 18 and 65 years old, had signed a written informed consent, were hospitalized and fulfilled the ICD-10 diagnostic criteria (World Health Organization (Ed.), 1992) for a major depressive episode (ICD-10: F31.3x–5x, F32, F33, F34, F38) or for a depressive disorder not otherwise specified (ICD-10: F39) as primary diagnosis. Patients were not included in the study if their depression had an organic cause, they possessed insufficient knowledge of the German language or the distance from their place of residence to the study centre was more than 100km. In total, 1073 patients took part in the study. Clinical diagnoses were generally assessed based on ICD-10 criteria administered by experienced and trained psychiatrists at admission and discharge. Diagnoses were confirmed utilizing the Structured Clinical Interview for DSM-IV (SKID-I) (Wittchen, Zaudig, & Fydrich, 1997). Comorbid axis II personality disorders were assessed with the Structured Clinical Interview for DSM-IV (SKID-II) (Wittchen et al., 1997). Overall, 759 patients were diagnosed with the SKID-II at admission. During the hospital stay patients were treated at the discretion of the psychiatrist in charge under consideration of the international clinical guidelines for the treatment of depression (American Psychiatric Association, 2000, Bauer et al., 2007; Deutsche Gesellschaft für Psychiatrie, 2000). Data was collected at admission and discharge as well as through biweekly observations during inpatient stay for selected measures. In addition, an annual follow-up was carried out for 4 years. For the present study, the general inclusion and exclusion criteria of the multicenter trial were applied with the exception of the diagnostic criteria which were tightened by only accepting patients with unipolar depressive disorders (ICD-10: F32, F33, F34). Of the total number of 119

patients which were excluded from the original data set, 69 patients did not meet the ICD-10 criteria for an unipolar depressive episode and for further 50 patients, the ICD-10 diagnosis was not reported resulting in a total data set of 954 patients (see Figure 1). In the present study, only data collected during the inpatient treatment period and at the one-year follow-up were analyzed.

Figure 1. Data selection and classification



5.2 Measures

5.2.1 Chronicity of depression

Chronic depression was defined as the presence of an unipolar affective disorder (depressive episode or dysthymia) for more than two years without a period of two months or longer with no symptoms (McCullough, 2003; Klein, 2008a). Cases were therefore classified as chronically depressed if they met at least one of two criteria at the time of admission: ICD-10 diagnosis F34.1 dysthymia or a duration of the current depressive episode of more than two years. The duration of the current episode was assessed via the basic assessment scale of clinical and socio-

demographic variables in psychiatry (BADO) (Cording, Gaebel, & Spengler, 1995) which was carried out at admission and discharge. The questionnaire comprises general sociodemographic aspects (e.g. employment status), personal items (e.g. critical life events) and past as well as current clinical information (e.g. family history of psychiatric disorders, length of current depressive episode). In the present study, 934 patients were assessed with the BADO at admission and 782 patients at discharge, respectively. For the remaining patients data for the BADO was missing. Applying the criteria of chronicity to the sample described above, 113 patients (11.8%) were categorized as chronically depressed. 57 of these chronically depressed patients had received the ICD-10 diagnosis F34.1 and 67 patients reported a depressive episode of more than two years. 11 patients fulfilled both criteria (ICD-10 diagnosis F34.1 and depressive episode lasting more than two years). In the group of individuals with dysthymia, the majority was diagnosed with a double depression (53 of 57 individuals with dysthymia were diagnosed with an additional unipolar affective disorder).

5.2.2 Depression severity

Depressive pathology was measured biweekly through two clinician-rated scales (Hamilton Depression Rating Scale (HAMD) (Hamilton, 1967); Montgomery Asberg Rating Scale (MADRS) (Montgomery and Asberg, 1979)) and one self-report questionnaire (Beck-depression-inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Beck, Steer, & Hautzinger, 1994)). The HAMD comprises 21 items, which cover affective, suicidal, physical as well as psychotic aspects of depression. For the present study, HAMD-17 scores were extracted from the 21-item version of the HAMD. HAMD-17 scores were classified according to the following commonly applied severity grading: remission (≤ 7), mild ($7<x<14$), moderate ($14\leq x<19$), severe (≥ 19) (Rush, First, Blacker, & American Psychiatric Association (Eds.), 2008; Henkel et al., 2011). For an estimation of suicital tendencies HAMD-17 item 3 (suicide) was analyzed separately. Scores of 1 or above were considered to indicate suicidal ideation (Pu, Setoyama, & Noda, 2017). The number of observed cases at admission, week 2, week 4, week 6, week 8, week 10, and at discharge for the HAMD was 949, 796, 587, 397, 272, 177, 768, respectively. The HAMD-17 was completed by 767 individuals both at intake and at discharge, thereof 92 were chronically depressed and 675 were nonchronically depressed. This subset was used for direct comparisons between admission and discharge (see table 9). The MADRS consists of 10 items including affective, cognitive and physical aspects of depression. The observed cases at

admission, week 2, week 4, week 6, week 8, week 10, and at discharge for the MADRS were 843, 710, 527, 364, 251, 162, and 699, respectively. The MADRS was completed by 697 individuals both at intake and at discharge, thereof 81 were chronically depressed and 616 were nonchronically depressed. This subset was used for direct comparisons between admission and discharge (see table 9). The 21-item self-report measure BDI assesses affective, physical and suicidal aspects of depression. The number of observed cases at admission, week 2, week 4, week 6, week 8, week 10 and at discharge for the BDI was 664, 560, 412, 283, 193, 115, and 534, respectively. The BDI was completed by 417 individuals both at intake and at discharge, thereof 47 were chronically depressed and 370 were nonchronically depressed. This subset was used for direct comparisons between admission and discharge (see table 9).

5.2.3 Personality characteristics

Personality disorders were assessed based on DSM-IV criteria as described above. In addition, the BIG FIVE personality domains neuroticism, extraversion, openness to experience, agreeableness and conscientiousness were administered at admission and discharge using the Neo-Five Factor Inventory (Neo-FFI) (Costa, P.T. & McCrae, R.R., 1992). The Neo-FFI is a 60-item self-report questionnaire, which captures each of the five personality domains with 12 items. 692 patients completed the Neo-FFI at admission and 514 patients completed the Neo-FFI at discharge. The Neo-FFI was completed by 480 patients both at intake and at discharge, thereof 49 were chronically depressed and 431 were nonchronically depressed. This subset was used for direct comparisons between admission and discharge (see table 9).

5.2.4 Social, occupational and physical functioning

Individual functioning was assessed via the following three clinician-rated scales: Global Assessment of Functioning Scale (GAF) (DSM-IV, Psychiatric Association, & American Psychiatric Association (Eds.), 2000), Social and Occupational Functioning Assessment Scale (SOFAS) (DSM-IV, Psychiatric Association, & American Psychiatric Association (Eds.), 2000), Clinical Global Impression rating scales (CGI) (Guy, 1976). The GAF assesses the level of functioning on a scale from 0 to 100. The highest score of 100 depicts the absence of symptoms as well as strong coping and social skills. Lower scores indicate relative impairments in these areas. 923 patients were rated on the GAF at admission and 770 patients at discharge, respectively. The GAF was completed by 759 individuals both at intake and at discharge, thereof

89 were chronically depressed and 670 were nonchronically depressed. This subset was used for direct comparisons between admission and discharge (see table 9). The SOFAS measures social and occupational functioning on a scale from 0 to 100. Lower scores refer to lower degrees of functioning. 919 patients were rated on the SOFAS at admission and 764 patients at discharge, respectively. The SOFAS was completed by 751 individuals both at intake and at discharge, thereof 89 were chronically depressed and 662 were nonchronically depressed. This subset was used for direct comparisons between admission and discharge (see table 9). The CGI rating scales assess symptom severity and treatment response on four items. For the present study only the item, measuring symptom severity on a 7-point scale was analyzed. In the present study, the number of observed cases at admission, week 2, week 4, week 6, week 8, week 10 and at discharge for the CGI were 943, 792, 587, 393, 274, 178, and 780, respectively. The CGI was completed by 774 individuals both at intake and at discharge, thereof 92 were chronically depressed and 682 were nonchronically depressed. This subset was used for direct comparisons between admission and discharge (see table 9).

5.2.5 Sociodemographic characteristics, personal and clinical history

Information on sociodemographic characteristics and clinical as well as personal history were collected via the BADO (see section 4.2.1).

5.3 Statistical analysis

The observed number of cases for each instrument and each time of measurement varied as noted above. The analyses presented in this article were based on the respective observed numbers. If not mentioned otherwise the analyses were based on the complete data set. Apart from the standard descriptive statistics, Fisher's exact test and t-tests were applied as appropriate. Due to the explorative approach, no adjustment was carried out for multiple t-tests. Standard deviations (sd) are reported in parentheses.

In order to receive an indication of the relative relevance of the observed variables for the chronicity of depression, logistic regression analyses were calculated. Variables with group differences of $p<.1$ were included in the comprehensive model. Measures, which combined data from several variables, were only added when none of the variables of which they were comprised of were part of the analysis. The comprehensive model was based on 445 observed

cases and included the following variables: gender, age, years of school, years of professional training, age at onset, age at first treatment, number of psychiatric disorders in the family, number of previous hospital stays, parents separated for more than one year/divorce before the age of 6, other comparably critical life events before the age of 6, patient separated from both parents for more than one year between the age of 6 and 15, other comparably critical life events between the age of 6 and 15, use of Benzodiazepines during current episode before admission, use of at least one psychotherapy type during current episode before admission, F40 diagnosis, F45 diagnosis, F13 diagnosis, an avoidant, dependent, obsessive-compulsive, negativistic, depressive, paranoid or borderline personality disorder and BDI, neuroticism and extraversion scores at admission. A stepwise regression was carried out with the comprehensive model in order to identify the most relevant variables for chronicity of depression. The effects of gender and age were controlled by including the respective variables in the model. Multicollinearity was analyzed by calculating variance inflation factors (VIF).

Repeated measurement ANOVAs were carried out to analyze change over time in clinical and personal characteristics. In the comparisons between admission and discharge only cases with observations both at admission and discharge were inserted in the repeated measurement ANOVAS and the respective Figures. In the analyses of biweekly data, the last observation carried forward (LOCF) method was used both in the Repeated Measurement ANOVAs as well as in the mean course graphs.

All statistical analyses were performed using the statistical software package R 2.15.2.

6 Results

This chapter portrays the results of the data analysis. The results and their implications are being evaluated in greater detail in the following discussion.

6.1 Sample Characteristics at baseline

6.1.1 Sociodemographic characteristics

The two groups did not significantly differ from each other in age or distribution of gender. The mean age in the group of chronically depressed patients was 44.3 (sd=10.7) and 45.1 (sd=12.2) in the group of nonchronically depressed patients (p=.47) (see Table 1). In both groups, the quota of women was elevated (chronic depression (cd): 58.4%, nonchronic depression (ncd): 63.1%, p=.35). The groups differed with respect to their employment status (Fisher test across all categories: p=.048; Fisher Test directly comparing retirement categories (retired regularly vs. retired on disability or early retirement) p=.033). A higher share of nonchronically depressed patients was employed (cd: 40.2%, ncd: 50.7%) or regularly retired (cd: 2.9%, ncd: 7.7%) and a higher share of chronically depressed patients was unemployed (cd: 33.3%, ncd: 25.9%) or retired on disability or early retirement (cd: 12.7%, ncd: 8.4%).

Table 1. Sociodemographic characteristics

Characteristic	Total sample	Chronic depression	Nonchronic depression	p[1]
Female, n (%)	597 (62.6)	66 (58.4)	531 (63.1)	.35
Age, mean (± SD)	45.0 (12.0)	44.3 (10.7)	45.1 (12.2)	.47
Years of school , mean (± SD)	10.6 (1.7)	10.8 (1.8)	10.5 (1.7)	.099
Years of professional training, mean (± SD)	3.2 (1.8)	2.9 (2.0)	3.3 (1.7)	.059
Years of education (school + professional training), mean (± SD)	13.8 (2.9)	13.7 (3.2)	13.8 (2.9)	.80
Marital status, n (%)				.70
Married	368 (40.4)	42 (38.9)	326 (40.6)	
Never married	260 (28.6)	31 (28.7)	228 (28.5)	
Widowed	29 (3.2)	4 (3.7)	25 (3.1)	
Divorced	105 (11.5)	14 (13.0)	91 (11.3)	
Not married. Living together	68 (7.5)	8 (7.4)	60 (7.5)	
Married. Living separately	74 (8.1)	7 (6.5)	66 (8.3)	
Other	6 (0.7)	2 (1.9)	4 (0.5)	
Employment status, n (%)				.048
Employed	435 (49.5)	41 (40.2)	394 (50.7)	
In training	46 (5.2)	8 (7.8)	38 (4.9)	
Unemployed	236 (26.8)	34 (33.3)	202 (25.9)	
Retired (regular)	63 (7.2)	3 (2.9)	60 (7.7)	
Retired (disability (applied or granted), early retirement)	78 (8.9)	13 (12.7)	65 (8.4)	
Unknown	21 (2.4)	3 (2.9)	18 (2.3)	

[1]Comparisons between nonchronic and chronic depressed persons, using Fisher tests for categorical variables and t-tests for continuous variables.

6.1.2 Clinical and personal history

Patients with chronic depression reported a significantly lower age at onset (cd: 28.8 (sd=14.7), ncd: 35.3 (sd=14.0), p<.001, see Table 2). In addition, a longer latency between onset and first treatment for the group of chronically depressed patients became apparent by combining the data on age at onset and age at first treatment (cd: 6.7 (sd=8.9), ncd: 3.2 (sd=6.5), p<.001). In the group of chronically depressed patients the cumulative number of psychiatric disorders in the family was significantly higher (cd: .79 (sd=.8), ncd: .63 (sd=.7), p=.046). Patients with chronic depression had also previously stayed significantly more often in a psychiatric hospital (cd: 1.73 (sd=2.7), ncd: .87 (sd=1.7), p<.01). The group of chronically depressed patients had received significantly more often Benzodiazepines before admission during the current episode (cd: 31.5%, ncd: 21.4%, p=.021). With respect to psychotherapy before the hospital stay during the current episode, a significantly higher share of chronically depressed patients had used at least one type of psychotherapy (cd: 42.3%, ncd: 28.7%, p<.01).

Table 2. Clinical history

Characteristic	Total sample	Chronic depression	Nonchronic depression	p[1]
Age at onset, mean (± SD)	34.5 (14.2)	28.8 (14.7)	35.3 (14.0)	<.001
Age at first treatment, mean (± SD)	38.2 (12.8)	35.9 (12.6)	38.5 (12.8)	.055
Years between onset and first treatment, mean (± SD)	3.6 (6.9)	6.7 (8.9)	3.2 (6.5)	<.001
Positive family history of psychiatric disorders				
Psychiatric disorders (≥1), n (%)	466 (49.8)	64 (57.7)	402 (48.8)	.086
Affective disorders, n (%)	285 (30.4)	39 (35.1)	246 (29.9)	.27
Suicides, n (%)	93 (9.9)	16 (14.4)	77 (9.4)	.13
Number of psychiatric disorders in the family, mean (± SD)	.65 (.8)	.79 (.8)	.63 (.7)	.046
Number of previous hospital stays, mean (± SD)	.98 (1.9)	1.73 (2.7)	.87 (1.7)	<.01
Medication classes before admission during current episode, n (%)				
Antidepressants (tri- & tetrazyclic)	299 (31.9)	39 (35.1)	260 (31.6)	.45
Selective Serotonin Reuptake Inhibitors SSRI	199 (21.3)	22 (19.8)	177 (21.5)	.80
Monoamine Oxidase Inhibitor	25 (2.7)	6 (5.4)	19 (2.3)	.11
Other Antidepressants	153 (16.3)	15 (13.5)	138 (16.8)	.49
Neuroleptics (total)	146 (15.6)	20(18.0)	126 (15.3)	.49
Neuroleptics (Second generation antipsychotic drugs)	33 (3.5)	4 (3.6)	29 (3.5)	1
Lithium	39 (4.2)	4 (3.6)	35 (4.3)	1
Other Mood Stabilizers	22 (2.4)	4 (3.6)	18 (2.2)	.32
Benzodiazepines	211 (22.5)	35 (31.5)	176 (21.4)	.021
Other Tranquilizers / Hypnotics	75 (8.0)	13 (11.7)	62 (7.5)	.14
Number of medication classes before admission during current episode, mean (± SD)	1.3 (1.3)	1.5 (1.5)	1.3 (1.3)	.10
Use of at least one psychotherapy type before admission during current episode, n (%)	283 (30.2)	47 (42.3)	237 (28.7)	. <.01
Location of treatment, n (%)				.060
University hospital	681 (71.3)	72 (63.7)	610 (72.4)	
District hospital	273 (28.6)	41 (36.3)	232 (27.6)	

[1]Comparisons between nonchronic and chronic depressed persons, using Fisher tests for categorical variables and t-tests for continuous variables.

The groups furthermore differed significantly with respect to critical life events they experienced during their childhood (see Table 3). A significantly higher share of patients in the group of chronically depressed patients experienced the separation of the parents for more than one year or a divorce (cd: 9.0%, ncd: 4.0%, p=.028) as well as other comparably critical life events (cd: 13.5%, ncd: 7.3%, p=.038) before the age of 6. The category “other comparably critical life

events" comprises physical, emotional and sexual abuse, which were not explicitly included as separate items in the questionnaire. Merging the questions on critical life events shows that a significantly higher share of chronically depressed patients experienced at least one critical life event before the age of 6 (cd: 28.8%, ncd: 17.0%, p<.01).

Table 3. History of critical life events

Characteristic	Total sample	Chronic depression	Nonchronic depression	p[1]
Critical life events before the age of 6, n (%)				
Death of the mother	13 (1.4)	3 (2.7)	10 (1.2)	.19
Death of the father	29 (3.1)	4 (3.6)	25 (3.0)	.77
Patient separated from both parents for more than one year	22 (2.5)	3 (2.7)	19 (2.3)	.74
Parents separated for more than one year / divorce	43 (4.6)	10 (9.0)	33 (4.0)	.028
Stay in a children's home for more than one year	14 (1.5)	1 (.9)	13 (1.6)	1
Stay with foster parents for more than one year	18 (1.9)	4 (3.6)	14 (1.7)	.26
Other comparably critical life events	75 (8.0)	15 (13.5)	60 (7.3)	.038
Number of critical life events before the age of 6, n (%)				.012
0	762 (81.6)	*79 (71.2)*	*683 (83.0)*	
1	143 (15.3)	*27 (23.4)*	*116 (14.1)*	
2	17 (1.8)	*2 (1.8)*	*15 (1.8)*	
≥ 3	12 (1.3)	*3 (2.7)*	*9 (1.1)*	
At least one critical life event before the age of 6, n (%)	172 (18.4)	32 (28.8)	140 (17.0)	<.01
Critical life events between the age of 6 and 15, n (%)				
Death of the mother	15 (1.6)	1 (.9)	14 (1.7)	1
Death of the father	27 (2.9)	5 (4.5)	22 (2.7)	.36
Patient separated from both parents for more than one year	21 (2.2)	5 (4.5)	16 (1.9)	.093
Parents separated for more than one year / divorce	54 (5.8)	8 (7.2)	46 (5.6)	.51
Stay in a children's home for more than one year	21 (2.2)	0 (0)	21 (2.6)	.16
Stay with foster parents for more than one year	19 (2.0)	3 (2.7)	16 (1.9)	.49
Other comparably critical life events	105 (11.2)	18 (16.2)	87 (10.6)	.080
Number of critical life events between the age of 6 and 15, n (%)				*.18*
0	717 (76.8)	*77 (69.4)*	*640 (77.8)*	
1	180 (19.2)	*29 (26.1)*	*151 (18.3)*	
2	30 (3.2)	*4 (3.6)*	*26 (3.2)*	
≥ 3	7 (.7)	*1 (.9)*	*6 (.7)*	
At least one critical life event between the age of 6 and 15, n (%)	217 (23.2)	34 (30.6)	183 (22.2)	.055

[1]Comparisons between nonchronic and chronic depressed persons, using Fisher tests for categorical variables and t-tests for continuous variables.

6.1.3 Clinical and personality characteristics at admission

The majority of patients were diagnosed with a severe depressive episode both in the group of chronically depressed patients (67.3%) as well as in the group of nonchronically depressed patients (61.8%) (See Table 8, appendix). The groups differed with respect to the share of moderate depressive episodes (cd: 25.7%, ncd: 35.2%, p=.045). A significantly higher share of chronically depressed patients suffered from a mental and behavioral disorder due to abuse of sedatives or hypnotics (F13) (cd: 5.3%, ncd: 1.2%, p<.01). In addition, a higher share of chronically depressed patients was diagnosed with a neurotic, stress-related and somatoform disorder (cd: 18.6%, ncd: 11.2% p=.029), with a somatoform disorder (F45) (cd: 6.2%, ncd: 2.3%, p=.026) and with a persistent somatoform pain disorder (F45.4) (cd: 6.2%, ncd: 1.2%, p<.01). Overall the group of chronically depressed patients was diagnosed with a significantly higher number of comorbid psychiatric disorders (cd: .65(sd=.84), ncd: .40(.77), p<.01). At admission, both groups presented on average clinically relevant scores regarding the degree of depression (HAMD-17, MADRS, BDI), psychosocial functioning (GAF, SOFAS) and the general clinical impression (CGI) (see Table 8, appendix). The BDI scores were significantly higher in the group of chronically depressed patients compared to nonchronically depressed patients (cd: 28.2 (sd=10.9), ncd: 25.3 (sd= 10.8), p=.024). Mean scores of the other measures (HAMD-17, MADRS, GAF, SOFAS) did not differ significantly between the groups.

In the group of chronically depressed patients the shares of a number of specific personality disorders were significantly elevated compared to the group of nonchronically depressed patients (Avoidant: cd: 25.0%, ncd: 13.6%, p<.01; Negativistic: cd: 8.0%, ncd: 2.4%, p=.012; Depressive: cd: 21.6%, ncd: 8.0%, p<.001; Paranoid: cd: 11.4%, ncd: 4.3%, p<.01) (see table 4). Combining the diagnoses in clusters showed significantly higher shares of cluster A (paranoid, schizoid, schizotypal) (cd: 13.6%, ncd: 5.7%, p<.01) and cluster C (avoidant, dependent, obsessive, compulsive) (cd: 38.6%, ncd: 25.0%, p<.01) diagnoses in the group of chronically depressed patients. The analysis also indicated that a higher share of patients in the group of chronically depressed patients was diagnosed with at least one personality disorder (cd: 46.6%, ncd: 34.0%, p=.024). The results of the NEO-FFI revealed a significantly higher level of neuroticism (cd: 2.8 (sd=.6), ncd: 2.5 (sd= .6), p<.01) and a significantly lower level of extraversion (cd: 1.5 (sd=.6), ncd: 1.7 (sd=.5), p<.01) in the group of chronically depressed patients (see table 4).

Table 4. Personality characteristics at admission

Characteristic	Total sample	Chronic depression	Nonchronic depression	p[1]
SKID II				
Specific personality disorder, n (%)				
Avoidant	113 (14.9)	22 (25.0)	91 (13.6)	.<.01
Dependent	45 (5.9)	9 (10.2)	36 (5.4)	.088
Obsessive-compulsive	105 (13.8)	18 (20.5)	87 (13.0)	.069
Negativistic	23 (3.0)	7 (8.0)	16 (2.4)	.012
Depressive	73 (9.6)	19 (21.6)	54 (8.0)	<.001
Paranoid	39 (5.1)	10 (11.4)	29 (4.3)	<.01
Schizotypal	4 (.5)	0 (0)	4 (.6)	1
Schizoid	17 (2.2)	3 (3.4)	14 (2.1)	.43
Histrionic	12 (1.6)	0 (0)	12 (1.8)	.38
Narcissistic	14 (1.8)	2 (2.3)	12 (1.8)	.67
Borderline	50 (6.6)	10 (11.4)	40 (6.0)	.066
Antisocial	9 (1.2)	1 (1.1)	8 (1.2)	1
Cluster A (Paranoid, schizoid, schizotypal), n (%)	50 (6.6)	12 (13.6)	38 (5.7)	<.01
Cluster B (Antisocial, borderline, histrionic, narcissistic), n (%)	71 (9.4)	11 (12.5)	60 (8.9)	.33
Cluster C (Avoidant, dependent, obsessive, compulsive), n (%)	202 (26.6)	34 (38.6)	168 (25.0)	<.01
One or more personality disorders, n (%)	269 (35.4)	41 (46.6)	228 (34.0)	.024
NEO-FFI, mean (±SD)[2]				
Neuroticism	2.6 (.6)	2.8 (.6)	2.5 (.6)	<.01
Extraversion	1.7 (.5)	1.5 (.6)	1.7 (.5)	<.01
Openness to experience	2.2 (.5)	2.3 (.5)	2.2 (.5)	.59
Tolerance	2.5 (.4)	2.4 (.4)	2.5 (.4)	.19
Conscientiousness	2.4 (.6)	2.4 (.6)	2.4 (.6)	.31

[1]Comparisons between nonchronic and chronic depressed persons, using Fisher tests for categorical variables and t-tests for continuous variables. [2]Out of the 692 patients 76 were chronically depressed individuals and 616 nonchronically depressed individuals.

6.1.4 Weighted characteristics of chronic depression at admission

In the logistics regression models – the comprehensive model as well as the reduced model, which resulted from the stepwise regression – the VIF values of all variables, were below 5 indicating that multicollinearity in the models was sufficiently low. The results of the stepwise regression (see Table 5) indicate that the strongest predictors of chronic depression were a low age at onset (OR=.93, p<.001), a relatively higher age at first treatment (OR=1.08, p=.010), fewer years of professional training (OR=.78, p=.014), consumption of Benzodiazepines (OR=3.04, p<.01) as well as the use of psychotherapy (OR=4.39, p<.001) during the current episode, the existence of a sedative, hypnotic, or anxiolytic related disorder (OR=13.44, p<.01), a depressive personality disorder (OR =4.31, p<.01) and a low degree of extraversion (OR=.48, p=.044).

Table 5. Adjusted Odds Ratios for Chronic Depression on baseline characteristics

Characteristic[1]	Odds Ratio (95% CI)[2]	p[2]
Age at onset	.93 (.90-.97)	<.001
Age at first treatment	1.08 (1.02-1.14)	.010
Number of previous hospital stays	1.16 (.95-1.41)	.13
Years of school	1.21 (.97-.1.50)	.088
Years of professional training	.78 (.64-.95)	.014
Benzodiazepines	3.04 (1.48-6.29)	<.01
Psychotherapy during current episode	4.39 (2.14- 9.36)	<.001
Comorbid psychiatric disorders		
Sedative, hypnotic, or anxiolytic related disorders (F13)	13.44 (2.01-88.20)	<.01
Phobic anxiety disorders (F40)	3.18 (.97-9.53)	.045
Somatoform disorders (F45)	4.46 (.71-21.66)	.079
SKID II - Specific personality disorder		
Depressive	4.31 (1.53-11.64)	<.01
NEO-FFI[3]		
Extraversion	.48 (0.23-.97)	.044

Result of stepwise regression (both). Complete cases: Chronically depressed: 51, Nonchronically depressed: 394. VIF <5, AIC: 269.12 [1]Characteristics which showed relevant group differences in the descriptive analysis (p<.1), [2]Adjusted for sex and age.

6.2 Treatment characteristics, course and outcome

6.2.1 Treatment characteristics

Chronically depressed patients were treated more often with Monoamine Oxidase Inhibitors (cd: 12.5%, ncd: 5.1%, p<.01) as well as with Lithium and other mood stabilizers (cd: 40.2%, ncd: 25.9%, p<.01) (see Table 6). The duration of hospitalization varied significantly between the groups. Chronically depressed patients stayed 81.3 days on average in the hospital compared to 59.5 days for nonchronically depressed patients (p<.01). In the group of chronically depressed patients, 21.2% stayed 100 days or more compared to 13.3% in the group of nonchronically depressed patients (Fisher test across all categories: p<.001).

Table 6. Treatment characteristics

Characteristic	Total sample n (%)/ mean (± SD)	Chronic depression n (%)/ mean (± SD)	Nonchronic depression n (%)/ mean (± SD)	p[1]
Medication classes applied during treatment, n (%)				
Antidepressants (tri- & tetrazyclic)	546 (58.6)	66 (58.9)	480 (58.5)	1
Selective Serotonin Reuptake Inhibitors (SSRI)	445 (47.4)	62 (55.4)	383 (46.7)	.088
Monoamine Oxidase Inhibitor	56 (6.0)	14 (12.5)	42 (5.1)	<.01
Other Antidepressants	529 (56.8)	68 (60.7)	461 (56.2)	.41
Neuroleptics (total)	397 (42.6)	46 (41.1)	351 (42.8)	.76
Neuroleptics (second generation antipsychotic drugs)	225 (24.1)	27 (24.1)	198 (24.1)	1
Lithium and other mood stabilizers	257 (27.6)	45 (40.2)	212 (25.9)	<.01
Benzodiazepines and other tranquilizers / hypnotics	694 (74.5)	81 (72.3)	613 (74.8)	.57
Electroconvulsive shock treatment (ECT), n (%)	*20 (2.6)*	*4 (4.3)*	*16 (2.3)*	*.28*
Use of at least one psychotherapy type during hospital stay, n (%)	481 (61.4)	58 (63.0)	423 (61.2)	.82
Duration of hospitalization (days), mean ± SD	62.1 (45.1)	81.3 (71.4)	59.5 (39.7)	<.01
Duration of hospitalization, n (%)				< .001
< 50 days	456 (47.7)	46 (40.7)	410 (48.6)	
< 100 days	364 (38.1)	43 (38.1)	321 (38.1)	
< 150 days	92 (9.6)	7 (6.2)	85 (10.1)	
< 200 days	23 (2.4)	6 (5.3)	17 (2.0)	
≥ 200 days	21 (2.2)	11 (9.7)	10 (1.2)	

[1]Comparisons between nonchronic and chronic depressed persons, using Fisher tests for categorical variables and t-tests for continuous variables.

6.2.2 Treatment outcome

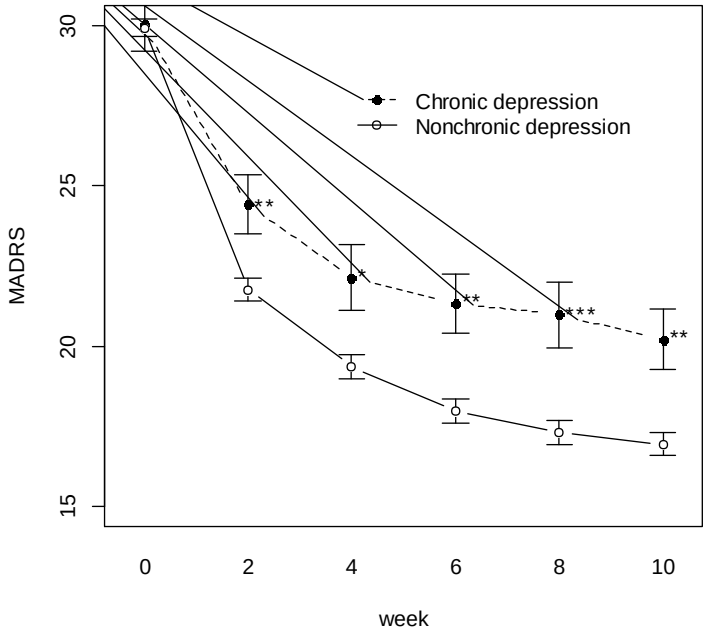
At discharge, all measures showed significant improvements compared to admission for both groups. This indicates that during the hospital stay the general condition of the majority of patients was significantly enhanced (see table 9, appendix). This effect was substantiated through the significant main effect "time" of the repeated measurement ANOVAs for the following measures: HAMD-17: p<.001, MADRS: p<.001, BDI: p<.001, GAF: p<.001, SOFAS: p<.001, NEO-FFI: neuroticism: p<.001, extraversion: p<.001, openness to experience: p<.01, agreeableness: p<.01, conscientiousness: p<.001 (see Table 9, appendix). Even though both groups improved on all measures, the rate of improvement differed on several clinician-rated measures, chronically depressed patients thereby exhibiting slower rates of change. These differences were evident through the significant interaction effects in the repeated measurement ANOVAs (HAMD 17: p<.01, MADRS: p<.001, CGI: p<.001, GAF: p=.001) as well as through the significant mean differences between the groups at discharge which were not observed at admission (HAMD 17: p<.001, MADRS: p<.001, CGI: p<.001, SOFAS: p<.01, GAF: p<.001). The differences between the group of chronically depressed patients and nonchronically depressed patients were also observed in the self-report measure BDI and parts of the Neo-FFI for which the main effect of the group was significant in the repeated measurement ANOVAs (main effect group: BDI: p<.01, Neo-FFI, Neuroticism: p=.015, Extraversion: p<.01). In addition part of the NEO-FFI maintained significant group differences at discharge (Neuroticism: cd: 2.5, ncd: 2.2, p<.01; Extraversion: cd: 1.7, ncd: 2.0, p<.01) (see Table 9 and Figure 3). In the detailed analysis of the HAMD-17 item 3 (suicide), the trend described above continued. For a significantly larger percentage of patients with chronic depression, suicidal ideation (HAMD-17 item 3 > 0) was reported at discharge compared to patients with nonchronic depression (cd: 29.3%, ncd: 11.9%, p<.001). Depression severity at discharge based on HAMD-17 ratings differed significantly between the groups which became especially clear by viewing remission rates of 39.1% for patients with chronic depression compared to 62.2% for patients with nonchronic depression (Fisher test across all categories: p<.001).

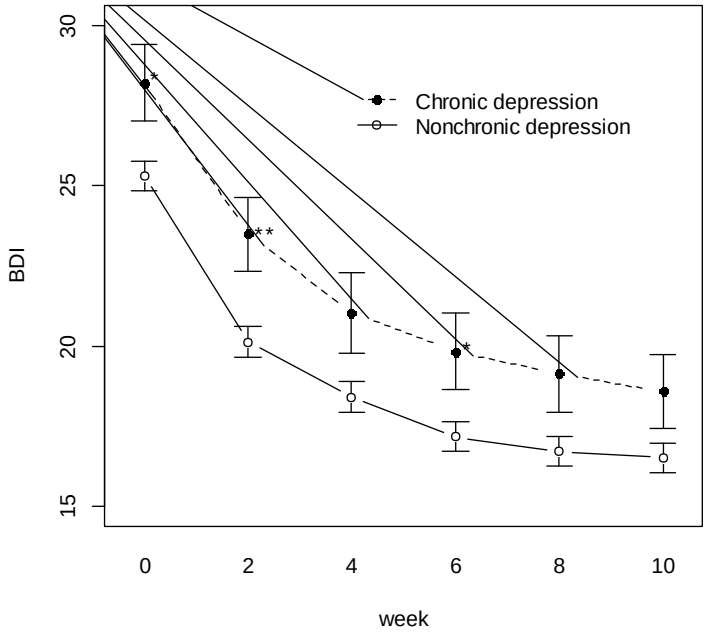
6.2.3 Treatment course

The measures collected on a bi-weekly basis detail the path to the treatment outcome described above. Figure 2 exemplarily shows the results for MADRS and BDI. In both groups, the strongest

reduction in pathology took place within the first two weeks followed by a further stepwise improvement. The main effect “time” was significant for all measures (Repeated measurement ANOVA (LOCF), main effect time: HAMD 17: $p<.001$, MADRS: $p<.001$, CGI: $p<.001$, BDI: $p<.001$). The two groups differed on the measures MADRS, HAMD 17 and CGI values in how fast the reduction in pathology advanced during the inpatient stay. In the group of chronically depressed patients symptom severity decreased at a slower rate on these measures as indicated by significant interaction effects (Repeated measurement ANOVA (LOCF), interaction effect: HAMD-17: $p<.01$, MADRS: $p<.001$, CGI: $p<.001$). The interaction for BDI values was not significant however in addition to the significant main effect “time” the main effect “group” was significant ($p<.01$) indicating differences between the groups. The mean scores of the HAMD-17, MADRS, CGI and BDI differed significantly at a number of data points: HAMD-17 (week 4: $p=.039$, week 6: $p=.012$, week 8: $p<.01$, week 10: $p<.01$), MADRS: (week 2: $p<.01$, week 4: $p=.013$, week 6: $p<.01$, week 8: $p<.001$, week 10: $p<.01$), CGI: (week 2: $p<.001$, week 4: $p<.001$, week 6: $p<.001$, week 8: $p<.001$, week 10: $p<.001$), BDI: (week 0: $p=.024$, week 2: $p<.01$, week 6: $p=.040$).

Figure 2. Plot of means of biweekly values for MADRS and BDI (LOCF)

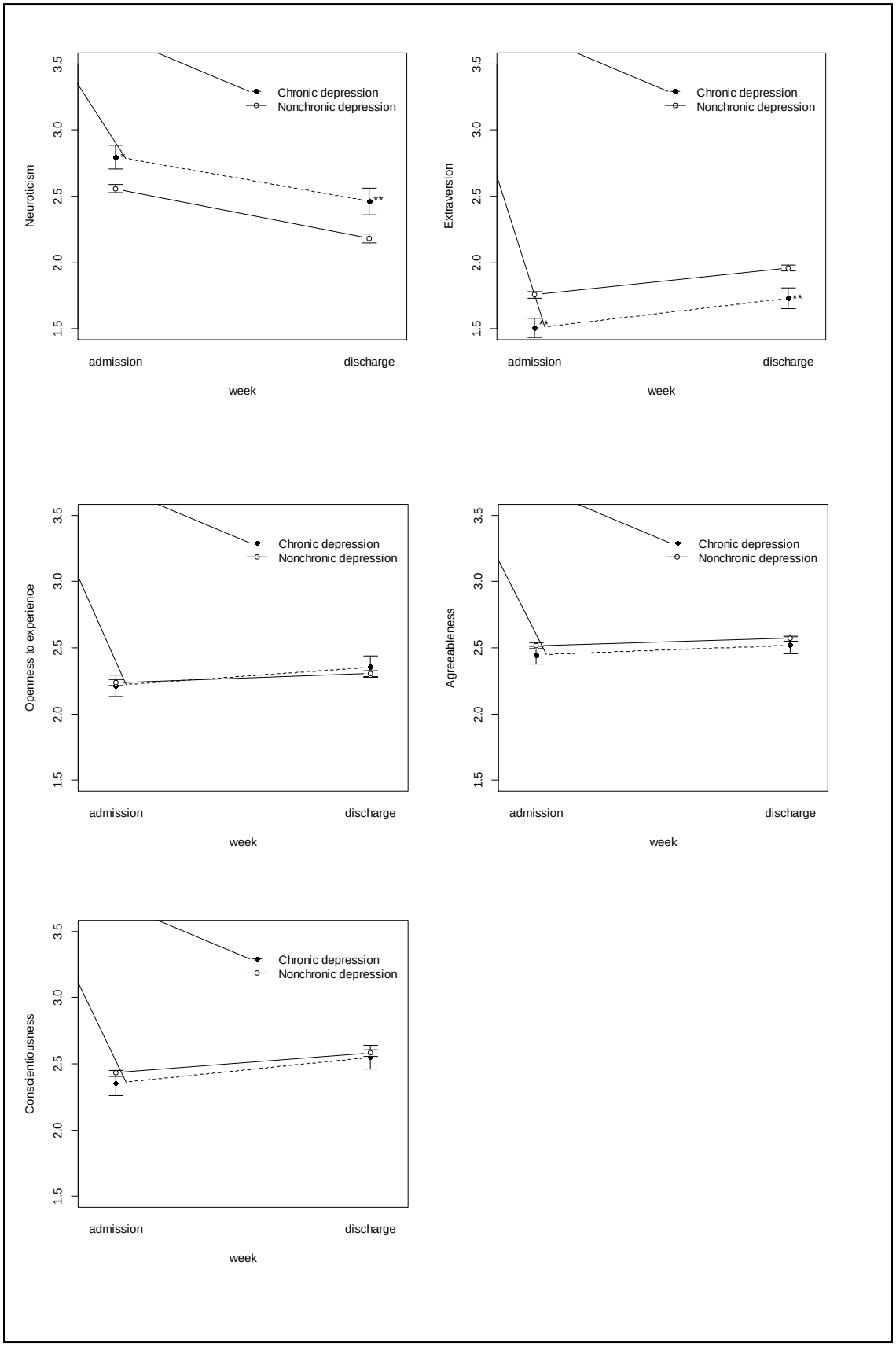




The asterisk symbol (*) indicates significant mean score differences at the respective weeks (* p<.05, ** p<.01, *** p<.001). MADRS: Repeated measurement ANOVA (LOCF): main effect time: p<.001, main effect group: p=.21, interaction: p<.001. BDI: Repeated measurement ANOVA (LOCF): main effect time: p<.001, main effect group: p=.0098, interaction: p=.20.

Figure 3 portrays the results for the subgroup of individuals who completed the NEO-FFI both at admission and at discharge (n = 480, cd:49, ncd: 431). In four of the five personality domains, the scores change significantly in the course of the hospital stay as is apparent via the main effect "time" in the respective repeated measurement ANOVA. In both groups, the levels of neuroticism declined and the levels of extraversion, openness to experience as well as conscientiousness increased. The results of the repeated measurement ANOVA showed significant differences for the main effect "group" for the domains extraversion and neuroticism. An interaction effect was not found for any of the domains.

Figure 3. Change in personality characteristics between admission and discharge



The asterisk symbol (*) indicates significant mean score differences at the respective weeks (* p<.05, ** p<.01, *** p<.001). Neuroticism: effects of the repeated measurement ANOVA: time: p<.001, group: p=.015, interaction: p=.68. Extraversion: effects of the repeated measurement ANOVA: time: p<.001, group: p<.01, interaction: p=.74. Openness to experience: effects of the repeated measurement ANOVA: time: p=.0011, group: p=.76, interaction: p=.26. Agreeableness: effects of the repeated measurement ANOVA: time: p<.01, group: p=.28, interaction: p=.71. Conscientiousness: effects of the repeated measurement ANOVA: time: p<.001, group: p=.36, interaction: p=.52.

6.3 Long term treatment outcome

The data on the one-year follow-up provide insights into the long-term development of the clinical and personality characteristics of the two groups. The results on the development of depressive symptomatology as measured by the HAMD 17 show that the two groups differed significantly at discharge from each other – chronically depressed individuals demonstrating a higher remaining amount of depressive symptoms (p<.01) (see table 7). The difference between the groups did not remain significant after one year even though a trend in the same direction is visible (p<.078). The results of the repeated measurement ANOVA also show no significant effect. Again, a trend is visible for the group effect (.074), the time effect (.083) as well as for the interaction effect (.053).

The results of the Neo-FFI measures show significant mean differences between the groups at discharge only for the dimension ‘extraversion’ in the subset of individuals for which data was available at both discharge and one-year follow-up (s. table 7). Chronically depressed individuals were significantly less extroverted compared to nonchronically depressed individuals (p=.031). At the one-year follow-up, the groups did not differ significantly from each other and the results of the repeated measurement ANOVA showed no significant effect. At the one-year follow-up, a small trend was visible indicating that individuals with chronic depression reported higher levels of neuroticism (p<.063) and lower levels of tolerance (p<.085). Compared to the previously reported data in table 4 this analysis only included individuals for whom data was both available

at discharge and at the one-year follow-up measurement resulting in 27 chronically depressed individuals and 203 nonchronically depressed individuals.

Table 7. Change in clinical and personal characteristics between discharge and one-year follow-up

	Discharge				One-year follow-up				Repeated Measurement ANOVA		
Characteristic	Total sample	Chronic Depress.	Non-chronic Depress.		Total sample	Chronic Depress.	Non-chronic Depress.		Effects		
	mean (± SD)			p	mean (± SD)			p	Interaction	Time	Group
HAMD 17[1], mean ± SD	7.48 (5.44)	9.93 (6.68)	7.17 (5.19)	<.01	7.48 (7.43)	9.27 (7.10)	7.24 (7.45)	.078	.053	.086	.074
NeoFFI[1], mean ± SD											
Neuroticism	2.18 (.70)	2.40 (.76)	2.15 (.68)	.12	2.11 (.79)	2.38 (.76)	2.08 (.79)	.063	.80	.31	.57
Extraversion	1.90 (.49)	1.68 (.55)	1.93 (.48)	.031	1.83 (.58)	1.65 (.64)	1.85 (.57)	.13	.75	.12	.22
Openness to experience	2.32 (.49)	2.36 (.63)	2.32 (.47)	.76	2.37 (.55)	2.42 (.67)	2.37 (.54)	.68	.92	.37	.92
Tolerance	2.59 (.42)	2.47 (.40)	2.60 (.42)	.13	2.63 (.48)	2.48 (.47)	2.65 (.48)	.085	.75	.31	.69
Conscientiousness	2.65 (.53)	2.65 (.56)	2.65 (.53)	.98	2.58 (.59)	2.63 (.48)	2.57 (.60)	.59	.72	.18	.81

[1] The analysis only included individuals for whom data was available at both points of measurement. This resulted in the following numbers. HAMD 17: cd n = 45, ncd n=351; NeoFFI: cd m = 27, ncd n = 203.

The results and their implications are being evaluated in greater detail in the discussion chapter.

7 Discussion

In the sections below the study results are summarized and the hypotheses and exploratory results are being discussed in detail. This detailed analysis is followed by an overall summary of the discussion.

7.1 Individual impairment

7.1.1 Symptom severity

Both groups did not differ with respect to depressive symptomatology at the time of admission except for the self-report measure BDI[1]. Both groups showed a significant reduction of symptom severity in the course of treatment[2]. At discharge, the majority of measures of depression severity (exception: BDI showing no significant differences) as well as the rate of suicidal ideation were higher in the group of chronically depressed individuals compared to nonchronically depressed individuals[3]. The remission rates at discharge were significantly higher for nonchronically depressed individuals compared to chronically depressed individuals[4]. The overall rate of clinical improvement was slower in the group of chronically depressed individuals[5]. No statistically significant differences between the groups were found at the one-year follow up[6].

The fact that no differences were observed in depression severity by the raters at intake might be due to the high rate of double depression and the thereby prevailing symptomatology of the current MDE in the group of the chronically depressed individuals. This finding is also in line with the results of Yang and Dunner (2001), Garvey et al. (1986) as well as Gilmer et al. (2005) who also did find no significant differences between groups of chronically and nonchronically depressed individuals.

It is interesting to note that the two groups did differ with respect to symptom severity on the self-report measure BDI. This might indicate that individuals with chronic depression experience

[1] see Table 8, appendix: affective disorder diagnosis, HAMD 17, MADRS, BDI, CGI, SOFAS, GAF.
[2] see Table 9: Repeated measurement ANOVA, main effect time: HAMD 17, MADRS, CGI, and BDI.
[3] see Table 9: mean difference of HAMD-17, Suicidal tendency (HAMD item 3), MADRS, CGI at discharge.
[4] see Table 9: depression severity (remission, mild, moderate, severe) based on HAMD17.
[5] see Table 9: Repeated measurement ANOVA, interaction effect: HAMD 17, MADRS, and CGI.
[6] see Table 9: mean difference of HAMD 17.

a greater burden, which is either not recognized by or not clearly expressed to an outside observer and therefore not displayed in observer ratings. The significant lower extraversion scores of chronically depressed individuals could be seen as a supportive argument for this line of thought. Forkmann et al. (2016) also found different results for self-report measures and observer-rated measures when assessing suicidal ideation in chronically depressed individuals using BDI as well as HAMD, respectively.

The great burden experienced by chronically depressed individuals which might be displayed in the self-report measures might be linked to the long duration of the depressive state and related psychosocial and occupational impairments. In future research, it might be interesting to further explore methodological influences on the measured symptomatology taking into account the specific characteristics of chronically depressed individuals.

The result that both groups experienced a significant improvement with respect to depressive symptoms is noteworthy. It shows that the inpatient treatment had a significant effect on the health status of the patients. The results of the follow-up measurement indicate that these improvements were stable even though the results have to be evaluated carefully due to a large drop-out rate between discharge and the one-year follow-up. It cannot be ruled out that the drop out was systematic and subgroups of chronically and nonchronically depressed individuals with a worse course were underrepresented in the follow-up sample.

The higher symptom severity of the chronically depressed individuals at discharge is in line with the results of Wiersma et al. (2011) and Klein et al. (1988b). Taking into account the observation that individuals with chronic depression stayed in the hospital significantly longer compared to nonchronically depressed individuals this difference appears even more pronounced. A longer period of time was required for individuals with chronic depression to reach a state, which still encompassed a higher symptom severity compared to nonchronically depressed individuals. This result is especially critical when taking into account the finding of Pintor, Torres, Navarro, Matrai, & Gastó (2004) who found that partial remission compared to complete remission was the strongest predictor of relapse over a 4-year period.

7.1.2 Suicidal ideation

The results indicate that chronically depressed individuals maintained a higher level of suicidal ideation compared to nonchronically depressed individuals at discharge[7].

The higher rates of suicidal ideation at discharge support the results reported by Angst et al. (2009). Unfortunately, no data was available in this study on the history of suicide attempts, which would have been interesting to compare to suicidal ideation tendencies. The results of Klein et al. (2008), Garvey et al. (1986) and Klein et al. (1988b) could therefore not be replicated. However, the reported tendencies for suicidal ideation indicate that suicidal tendencies are a common characteristic of chronic depression, which appears to be even more pronounced, compared to nonchronic depression. The increased suicidal tendency in chronically depressed individuals has to be taken very seriously especially when taking into account the low extraversion scores, which are indicating a low inclination and possibly competence to communicate the despair to others, and the long periods during which the suicidal ideation takes place given the long-term nature of chronic depression.

7.1.3 Psychosocial functioning

At admission, chronically depressed individuals and nonchronically depressed individuals both experienced severe social and occupational impairment and did not differ significantly from each other. At discharge, chronically depressed patients experienced greater social and occupational impairment compared to nonchronically depressed patients[8]. Measures of social and occupational functioning showed a significantly slower rate of change for one of the two measures (GAF) for chronically depressed individuals compared to nonchronically depressed individuals.

The results are in line with the results of Rhebergen et al. (2010) and Agosti (2014). Both studies reported lower levels of psychosocial functioning after remittance from chronic depression.

[7] see Table 9: mean difference suicidal tendency (HAMD item 3) at discharge.
[8] see Table 9: mean difference of SOFAS, GAF at admission and discharge.

We did not differentiate between subgroups of chronically depressed individuals. Therefore, it was also not differentiated between possible differences among subgroups of chronically depressed individuals with respect to psychosocial functioning as was shown by Leader and Klein (1996) as well as by Yang and Dunner (2001). The comparably low levels of psychosocial functioning of the two observed groups (chronically and nonchronically depressed individuals) stresses that the individuals of both groups were severely impaired at the time of admission which might be a sample specific characteristic due to the inpatient population of the study.

The difference in psychosocial functioning between the two groups at discharge highlights the effects and burden of chronic depression on the individuals. Further research might explore the different dimensions of psychosocial functioning in greater detail. It might be interesting to compare the rates at which different aspects of social and occupational functioning decline or improve respectively during the course of chronic depression including the time before the onset and after the remission of the chronic depression. The interaction of the level of social and occupational activity with the course of chronic depression might provide valuable insights especially for the prevention and treatment of chronic depression.

7.1.4 Comorbidity

Individuals with chronic depression were diagnosed with a higher number of comorbid psychiatric disorders and specifically more often with a mental and behavioral disorder due to abuse of sedatives or hypnotics as well as with a neurotic, stress-related and somatoform disorder[9]. In the subcategories, they were diagnosed more often with a somatoform disorder (F45) and hereby more often with a persistent somatoform pain disorder (F45.4). The results for the other subcategories such as specific anxiety disorders were not significant even though a trend was visible for social phobias (F40.1). Additionally, chronically depressed individuals were diagnosed more often with an avoidant, negativistic, depressive as well as a paranoid personality disorder compared to nonchronically depressed individuals.

The elevated levels of benzodiazepine abuse (mental and behavioral disorder due to abuse of sedatives or hypnotics) found in this study are in line with the results of Angst et al. (2009) as

[9] see Table 7, appendix.

well as with a trend for generally higher rates of substance abuse reported by Hölzel et al. (2011). Since benzodiazepines are mainly anxiolytic agents it might be speculatetd that the elevated level of abuse in chronic depressed patients leads to an underestimation of anxiety disorders in that subgroup. The trend towards elevated levels of social phobia is also in line with the results of Angst et al. (2009). However opposing to the results of Klein et al. (1988b) and Rhebergen et al. (2010) as well as Wiersma et al. (2011) the current data did not clearly show generally elevated levels of anxiety disorders for the group of chronically depressed individuals compared to nonchronically depressed individuals.

The slightly higher share of chronically depressed individuals with a social phobia as well as the higher share of individuals with an avoidant, negativistic, depressive or paranoid personality disorder underline the difficulties in social interaction which chronically depressed individuals experience. This comorbid pattern of social phobia and the described set of personality disorders appear to support the treatment rationale of the CBASP approach developed by McCullough (2003). In his approach, McCullough names an interpersonal avoidance pattern as one of the key characteristics of chronically depressed individuals, which he targets with his combination of interpersonal and cognitive psychotherapy.

As Klein et al. (1988a), the results also showed elevated levels of personality disorders in the group of chronically depressed individuals compared to nonchronically depressed individuals. However, the pattern of these data differed from their results. Klein et al. (1988a) reported elevated levels of borderline, antisocial and schizotypal personality disorders whereas in the data set at hand individuals with chronic depression were diagnosed more often with avoidant, negativistic, depressive as well as paranoid personality disorders compared to nonchronically depressed individuals. Riso et al. (2003) reported higher levels of personality disorders on a general level. Klein et al. (1999a) also found higher levels of personality disorders and elevated levels of cluster C personality disorders for individuals with early-onset chronic depression compared to individuals with late-onset chronic depression. The elevated levels of cluster C personality disorders are more in line with the pattern found in the data of the present study. The results of an analysis of a subsample of this sample reported no differences in personality disorders among the groups of chronically and nonchronically depressed individuals (Köhler et al.; 2015). This result may be due to the specifics of the subsample, which only included

individuals who had agreed to participate in a specific pharmacological treatment algorithm. Individuals with a personality disorder might have been less likely to agree to this sort of treatment.

The current results therefore generally support the body of research in the sense that individuals with chronic depression tend to be diagnosed more frequently with a personality disorder. With respect to the pattern of personality disorders, the results are mixed. These differing results might also be indicators for different subgroups of chronically depressed individuals with different paths leading to the chronically depressed state and the comorbid personality disorder. When treating depression in general the existence of a personality disorder has to be taken into account since it appears to impact treatment effects (Unger, Hoffmann, Köhler, Mackert, & Fydrich, 2013). With the elevated levels of personality disorders, this appears to be specifically relevant for individuals with chronic depression.

The number and kind of comorbid nonpsychiatric medical illnesses have not been assessed in this study. This would have been an interesting additional factor specifically to interpret the reported higher levels of somatoform disorders and the tendency of higher rates of persistent pain disorders. A number of studies have found higher rates of medical illnesses (Wiersma et al., 2011; Gilmer et al., 2005) and specifically pain (Angst et al. 2009) in the group of chronically depressed individuals. For further research, it might be interesting to explicitly explore the relationship between medical illnesses, mental and behavioral disorders due to abuse of sedatives or hypnotics and chronic depression.

The general result – that individuals with a chronic depression exhibit a greater number of comorbid psychiatric disorders on top of the sufficiently severe condition of a chronic depression is a relevant finding, which is in line with the majority of previous studies many of which are listed in the systematic review by Hölzel et al. (2011). This result highlights the burden of this group of individuals. As mentioned above this finding does not include any indications with respect to the past interaction of the disorders with each other or to their order of appearance. What has been found however in previous research by Klein et al. (2008) as well as by Garcia-Toro et al. (2013) is that comorbid psychiatric disorders appear to impair the course of the chronic depression.

For further research in the area of comorbidity among individuals with chronic depression, it might be interesting to investigate individual clinical histories examining possible patterns and subgroups of chronically depressed individuals. There might be a subgroup for which a chronic medical condition or chronic psychiatric disorder played a vital role in the development of a chronic depression. In some cases, the chronic depression might have appeared beforehand or might moderate the experienced symptomatology of the comorbid disorders.

7.2 Personality characteristics

On all domains of the Neo-FFI, significant change took place in the course of the inpatient stay. Individuals with chronic and nonchronic depression showed decreased levels of neuroticism and increased levels of extraversion, openness to experience, tolerance as well as conscientiousness at the end of the inpatient stay. Group differences were found in the levels of the domains neuroticism and extraversion at admission and discharge. The group of chronically depressed individuals displayed higher levels of neuroticism as well as lower levels of extraversion at admission as well as at discharge compared to nonchronically depressed individuals. In the regression model, only extraversion remained as a significant predictor of chronic depression.

The results regarding the change during the inpatient stay validate the results of Ormel et al. (2004) who reported an influence of depressive symptomatology on personality traits for individuals with MDE. The results furthermore indicate that personality domains are influenced by depressive symptomatology both for chronically and nonchronically depressed individuals. Furthermore, the data show that a positive change took place at a comparable rate for both chronically and nonchronically depressed individuals albeit from different initial levels. Based on the results of Ormel et al. (2004) it can be hypothesized that the score at discharge for individuals who have achieved remission represents their respective premorbid level. The lower remission rates in the group of chronically depressed individuals might explain the differences between the groups at discharge. This line of thought however does not explain the initial differences between the two groups at admission.

The fact that the two groups already differed significantly from each other at admission on the domains neuroticism and extraversion is generally in line with the results reported by Wiersma et

al. (2011) and Robison et al. (2009). They both found differences between the groups of chronically and nonchronically depressed individuals with respect to neuroticism and extraversion. As in the current sample sample, the predictive power of extraversion within a regression model proved to be stronger compared to neuroticism indicating that extraversion is a more pronounced differentiating characteristic between the two groups.

These results oppose the results of Hirschfeld et al. (1986) and Weissmann et al. (1978) to some extent who found neuroticism and not extraversion to possess predictive power for the chronic course of a depressive episode.

Taking the sample size of the studies into account it can be stated that all studies except for the study conducted by Wiersma et al. (2011) who included 1002 individuals consisted of samples with less than 200 individuals in total. Additionally the study of Wiersma et al. (2011) simultaneously applied the NEO-FFI questionnaire as a measurement of personality domains whereby the other studies used other personality inventories such as the Maudsley Personality Inventory (Eysenck, 1959). The fact that Wiersma et al. (2011) reported comparable results with a similar sample size using the same personality inventory however in an outpatient sample strongly supports the validity and robustness of the current findings on the importance of extraversion for the differentiation between chronically and nonchronically depressed individuals.

Within the group for which katamnestic data was available significant differences between chronically and nonchronically depressed individuals at discharge were only apparent in the domain extraversion. At the one-year follow-up date there were no significant differences between the former groups of chronically and nonchronically depressed individuals. On a trend level individuals from the group of chronically depressed individuals scored higher on the domain of neuroticism compared to individuals from the group of nonchronically depressed individuals.

The katamnestic results of the NEO FFI have to be interpreted with great caution since only a small subsample of the original sample participated in the one-year follow-up. The resulting small numbers (chronically depressed: 27, nonchronically depressed: 203) have less statistical power to demonstrate possible differences between the groups. Furthermore it cannot be ruled out

that a systematic drop out took place whereby subgroups of chronically or nonchronically depressed individuals were over- or underrepresented in the one-year follow-up sample.

The results that the groups of chronically and nonchronically depressed individuals in this small subsample differ with respect to extraversion at discharge and that they differ on a trend level with respect to neuroticism at the one-year follow-up indicates that extraversion plays a stronger role in differentiating between the two groups in severe periods of depression. Neuroticism might be a domain differentiating the groups of chronically and nonchronically depressed individuals rather in periods in which chronically depressed individuals experience less severe depressive symptoms and individuals with nonchronic depression are in complete or partial remission. Neuroticism might therefore be a "trait marker", which reflects stable differences between individuals with chronic and nonchronic forms of depression whereas extraversion might rather be a state dependent marker. The data reported by Wiersma et al. (2011) were collected from an outpatient sample of individuals who were diagnosed with a major depressive episode at the time of data collection. This represents a severely impaired subgroup of chronically depressed individuals comparable to the current sample at admission. The pronounced role of extraversion in both samples at a comparable moment in the course of depression supports the hypothesis that chronically depressed individuals tend to react with a stronger reduction of extraversion compared to nonchronically depressed individuals in periods when depressive symptoms of the chronically depressed individuals are especially strong, in this case justifying an inpatient stay. From a long term perspective, focusing on the course of depression, neuroticism might be a more decisive differentiating factor for chronic and nonchronic depression. This would explain the opposing study results described above and be in line with the results reported by Weissmann et al. (1978) and Hirschfeld et al. (1986) who found neuroticism to predict the chronic course of a depression. For future research, it would be interesting to further explore the role of the two domains neuroticism and extraversion with respect to possibly varying roles in different phases of chronic and nonchronic depression, respectively.

7.3 Personal history and childhood adversity

We expected individuals with chronic depression to have experienced a greater number of adverse childhood events compared to nonchronically depressed individuals. The results support

the hypothesis to some extent. A larger share of chronically depressed individuals has experienced at least one critical life event before the age of six compared to nonchronically depressed individuals. Chronically depressed individuals have experienced more often the separation of their parents as well as other comparably critical life events both before the age of six. Individuals with chronic depression have also experienced a higher absolute number of critical life events before the age of six compared to individuals with nonchronic depression. Significant differences between the groups were found neither for further adverse life events before the age of six nor for adverse life events between the age 6 and 15.

The differences found in the category separation of their parents is contrary to the results of Wiersma et al. (2009) who did not find elevated levels of divorced parents in the group of chronically depressed individuals. Angst et al. (2011) however reported family problems as a risk factor for the development of chronic depression. The further results on childhood life events (parental loss, separation from home) reported by Wiersma et al. (2009) was in line with the current results with no significant differences between the two groups.

The fact that the groups differed only in the adverse childhood events experienced before the age of 6 accentuates the vulnerability of early childhood and its important role in the development of an individual vulnerability for chronic depression in the future.

The current study was unable to validate the higher share of childhood trauma reported by Wiersma et al. (2009) in detail. Physical, psychological and sexual abuse as well as emotional neglect was not assessed separately. The information on these traumatic experiences might be found in the accumulative category “other comparably critical life events”. The higher share of chronically depressed individuals who affirmed this category compared to nonchronically depressed individuals might be an indication for elevated levels of traumatic life events of chronically depressed individuals compared to nonchronically depressed individuals. In order to make a reliable deduction it would have been essential to assess the information via a reliable and valid instrument such as the Childhood Trauma Interview (Fink et al., 1995).

The current study also did not assess the quality of maternal and paternal relationships experienced by chronically and nonchronically depressed individuals which has been reported as a risk factor for both the development (Angst et al., 2011) and the course of chronic depression

(Klein et al., 2008). Future research assessing all aspects of adverse childhood experiences within one sample comparing healthy controls, nonchronically depressed as well as chronically depressed individuals might be able to shed further light on the role of adversity on the development and course of depression and its chronicity. As Klein, Roniger, Schweiger, Späth, & Brodbeck (2015) investigated in their study it might be valuable to further explore the relationship between childhood adversity, personality disorders and chronic depression, preferably in prospective studies.

In the previous sections the factors with defined hypotheses were discussed. In the following section the results of the explorative analysis of the data will be discussed and evaluated within the current body of research.

7.4 Explorative results

7.4.1 Prevalence

The share of chronically depressed individuals in the complete sample was 11.8%. This is less than has been reported in other large samples such as Gilmer et al. (2005) and Wiersma et al. (2011) who classified a share of 21.2% and 31% respectively as chronically depressed. The lower rates of this study might be due to the nature of the inpatient sample. Patients who are admitted into a psychiatric hospital generally present severe depressive symptoms. Based on the hospital admittance criteria the subgroup of chronically depressed individuals who are experiencing milder depressive symptomatology, such as a dysthymic disorder, might be underrepresented in the sample. However, the majority of individuals with a severe depression or suicidal ideation do not require inpatient treatment. It is therefore interesting to see that the two groups of depressed individuals – chronically and nonchronically depressed individuals – who both require inpatient care still show significant differences on a variety of factors even though the initial rational for inpatient treatment might have been similar (severe depressive symptomatology, suicidal ideation).

7.4.2 Sociodemographic characteristics

The distribution of age, gender and marital status was similar within the groups. Individuals with chronic depression reported a more disruptive work history (higher unemployment, higher rates of disability or early retirement). The years spent with school and professional training did not differ significantly.

The comparable distribution of gender is in accordance with the results of Wiersma et al. (2011) and Gilmer et al. (2005) as is the higher share of women in both groups. Both studies however reported a higher age on average for individuals with chronic depression, which has not been found in this study. Hölzel et al. (2011) reported in their systematic review of risk factors for chronic depression inconsistent results with respect to age. With respect to years spent with education Wiersma et al. (2011) and Angst et al. (2009) also reported no differences between the two groups contrary to Gilmer et al. (2005) who reported slightly less years of education for chronically depressed individuals. In the study by Gilmer et al. (2005), unemployed individuals were more likely to have a chronic depression compared to employed individuals. Angst et al. (2009) reported similar results, which is in accordance with the results of the present study. Based on the results and the body of research it appears that the effect of chronic depression compared to nonchronic depression is stronger on the job history compared to the educational performance. This might be due to the fact that the average age at onset was 28.8 years for chronically depressed individuals and 35.3 years for nonchronically depressed individuals indicating that for a majority of individuals the symptoms started after completing their education. It also appears reasonable that chronically depressed individuals who experience clinically significant depressive symptoms as well as significant impairments in social and occupational functioning both over a long period of time encounter a greater amount of difficulties in their personal work history compared to individuals with nonchronic depression who experience these difficulties over shorter periods of time. It might be easier to continue or resume a job given the temporary impairments accompanying a nonchronic depressive episode compared to the long-term impairments accompanying chronic depression. Hereby the results of Mueller et al. (1996) as well as Garcia-Toro et al. (2013) are notable showing that the majority of individuals with a chronic depression recover at some point in time, which is encouraging for both patients and their family as for their employers.

7.4.3 Onset

Individuals with chronic depression reported a lower age at onset and a longer latency between onset and first treatment.

The lower age at onset is in line with the results found by Garcia-Toro et al. (2013), Klein et al. (1988a) as well as Garvey et al. (1986). What was additionally interesting was the longer latency between onset of depressive symptoms and first treatment, a finding that was also reported by Garcia-Toro et al. (2013). This finding indicates that a fast treatment following the first onset of a depression plays a vital role in the prevention of chronic depression. It also stresses the strong effect the onset of a depression can have early in life being followed more often by a chronic course when it arises early.

An early onset of depressive symptoms can also be viewed as a consequence of a combination of adverse factors being present in an individual's life. The number, the nature or specific combination of factors might then play a role in determining whether the depression remains episodic or becomes chronic. As the results on personal factors show, chronically depressed individuals appear to carry a greater burden with respect to critical life events, which might explain the differences with respect to age at onset to some extent. The study results of van Randenborgh, Pawelzik, Quirin, & Kuhl (2016) also underline the role age at onset plays in the realm of chronic depression. They found individuals with chronic depression with an early onset to have lower implicit self esteem compared to individuals with chronic depression with a late onset as well as compared to individuals with episodic depression.

Additionally it certainly has to be taken into account that the information on age at onset were based on self report data which is naturally to some extent prone to cognitive distortions which might be accentuated in a depressed state of mind. Since the extent of depressive symptomatology however did not differ between the groups at the time of admission where the information on the age at onset were collected it is hypothesized that a possible distortion in memory was comparable in both groups and does not explain the differences between the groups.

7.4.4 Health care utilization

Chronically depressed individuals have stayed significantly more often in a psychiatric hospital in the course of their lifetime compared to nonchronically depressed individuals. They also stayed significantly longer in the psychiatric hospital at the stay observed in the current study.

These results are in line with the results of Garcia-Toro et al. (2013), Villoro et al. (2016) and Yang and Dunner (2001) who all found higher rates of health care utilization for chronically depressed individuals. This study hereby adds information to the research body with respect to length of inpatient stay, which was explicitly called for by Hölzel et al. (2011) in their systematic review.

The results of the present study are additionally interesting since chronically depressed individuals stayed on average more than 20 days longer in the hospital while their health status at discharge was still worse compared to nonchronically depressed individuals with significantly higher ratings of depressive symptomatology as well as lower levels of social and occupational functioning.

From a societal view, these frequent and long hospital stays imply significant costs. In combination with the higher unemployment as well as higher rates of disability or early retirement for chronically depressed individuals reported above the financial burden posed by chronic depression for society appears significant.

For further research on treatment options for individuals with chronic depression it would therefore be interesting to include differentiated long term cost benefit analyses. Taking into account all expected costs and lost incomes both to society and to the individual might be a worthwhile perspective. This perspective might further support research on effective treatment options and assist in justifying complex and long term treatment options, which apart from easing the burden of chronic depression also reduce the financial impact of the illness.

7.4.5 Family history and biological factors

The share of individuals with a positive family history of psychiatric disorders and specifically affective disorders and suicides did not differ significantly between the two groups. There was a tendency that a higher share of individuals with chronic depression reported a positive family history of psychiatric disorders. In addition, individuals with chronic depression reported a higher number of psychiatric disorders in their families on average.

Contrary to the outcome of the systematic review by Hölzel et al. (2011) who reported a family history of mood disorders as a risk factor for chronic depression, the current study found no differences between the groups with respect to a positive family history for affective disorders. The present results are however in line with the results reported by Garvey et al. (1986), Angst et al. (2009) as well as Yang and Dunner (2001) who also did not detect significant differences between the groups with respect to affective disorders in first degree relatives. The different results of the studies might be due in part to different subgroups of chronically depressed individuals as well as different subgroups of nonchronically depressed individuals. Since it was an inpatient sample, the nonchronically depressed group in this study might have been a specifically severely depressed subgroup with a higher number of risk factors present compared to an outpatient sample.

The elevated number of psychiatric disorders indicates – however unspecifically – that the two groups differed from each other with respect to the extent by which they were affected by psychiatric disorders within their families. Neither clear biological mechanisms (Riso et al. 2002) nor genetic models (Klein, 2008b) specific for chronic depression compared to acute depression and their transgression across generations have been validated so far. The presence of psychiatric disorders in a family might present a biological as well as social risk factor for the development of an affective disorder. The extent of the burden imposed by the positive family history of psychiatric disorders might play a role for the probability of the development of an affective disorder and its severity as well as chronicity.

Future research including neurobiological information is needed to explore the role of a positive family history of psychiatric disorders in greater detail.

7.4.6 Treatment

Individuals with chronic depression had taken significantly more often Benzodiazepines and had used more often psychotherapy before being admitted to the hospital for the current study. Apart from benzodiazepines, both groups did not differ with respect to the medication classes they received before being admitted to the hospital for the current study. In the course of treatment, they were treated with a greater variety of medication classes (Monoamine Oxidase Inhibitors, mood stabilizers) and they spent significantly more days at the hospital at the stay under study. Apart from the Monoamine Oxidase Inhibitors and mood stabilizers, which the group of chronically depressed individuals received more often in the course of treatment, the groups did not differ with respect to the applied medication classes, psychotherapy as well as number of Electroconvulsive shock treatments they received during their hospital stay.

The results are in line with the data analyzed by Angst et al. (2009) who also found chronically depressed individuals to have taken benzodiazepines more often as well as to have consulted psychologists more often compared to nonchronically depressed individuals. Angst et al. (2009) additionally found significant differences between the two groups with respect to further treatments such as antidepressants, hypnotics and neuroleptics. These findings validate the results of the inpatient stay of the current study, which showed a greater variety of medication classes prescribed to chronically depressed individuals.

Summarizing the results of this study it appears that within a naturalistic setting with an individualized treatment at the discretion of the respective medical team in charge, it is possible to reach significant improvements in chronically depressed individuals. The number of applied medication classes required to reach this improved state appears to be larger compared to nonchronically depressed individuals and the time required appears to be longer.

With respect to psychotherapy, the results showed that both groups received similar psychotherapeutic attention. Due to the naturalistic setting, no specific psychotherapy focusing on the needs of chronic depression was delivered to the group of chronically depressed individuals. Several studies indicate that CBASP is a type of psychotherapy which produces significant effects for individuals with chronic depression both in an outpatient setting (Keller et al., 2000) as well as in an inpatient setting (Brakemeier et al., 2015; Schramm, Hautzinger, Zobel,

Kriston, Berger, & Härter, 2011). Assessing chronicity before admission and allocating individuals to institutions offering CBASP programs might further improve treatment effects for chronically depressed individuals. In addition to effective inpatient psychotherapy, it is relevant to ensure long term psychotherapeutic treatment in order to stabilize and maintain treatment effects (Brakemeier et al., 2015).

An analysis by Köhler et al. (2015) with a subsample of the data of this study, which followed a treatment algorithm of antidepressants (for details see Köhler et al., 2015), found no pattern indicating superior treatment strategies among the applied strategies.

Sung et al. (2012) however did not find significant differences between chronically and nonchronically depressed individuals with regard to the effect of varying pharmacological treatment strategies.

Generally, pharmacotherapy appears to be effective in the treatment of chronic depression even though a superior pharmacological treatment strategy for chronic depression has not yet been found, improvement takes longer compared to nonchronic depression and remission rates are not yet satisfactory. This stresses the relevancy of long term continued pharmacotherapy treatment in order to reach remission or to maintain the achieved status. This was also pointed out by Kocsis (2003) in a review on pharmacotherapy for chronic depression in which he called for more research on augmentation strategies, sequential algorithms of treatment and psychotherapy.

7.4.7 Long-term development

At the one year katamnesis, the two groups did not differ significantly from each other with respect to depressive symptomatology as measured by the HAMD17. On a trend level there was an interaction effect visible – chronically depressed individuals showing slightly less symptoms over time while nonchronically depressed individuals remained almost at the same status albeit at a lower level.

When interpreting the results of the katamnestic data the high drop out rate has to be taken into account. Only 37.8% of individuals who participated in the study took part in the study one year

after their discharge from the psychiatric hospital. It cannot be ruled out that the drop-outs systematically differed from the group who participated at the katamnesis. It can be hypothesized that individuals with a high remaining depressive symptomatology were less motivated to participate possibly resulting in systematically distorted katamnestic results.

The stability of the depressive symptomatology over time within the observed subgroup however is notable especially for the group of chronically depressed individuals. It indicates that on average the achieved improvement in depressive symptoms was sustainable. This is also in line with the results of Garcia-Toro et al. (2013) and Mueller et al. (1996) who showed that a large share of individuals recovers from chronic depression when followed up over a long course of time.

It would have been interesting to analyze the long term development of the chronically depressed individuals in the sample under study over the course of several years. However, due to very high drop out rates and a medium sized initial sample these analyses were not possible.

7.5 Summary and Conclusion

At admission of the inpatient stay observer-rated measures of acute depressive symptomatology (HAMD 17, MADRS) and of social and occupational functioning (GAF, SOFAS, CGI) were similar in the two groups (chronically vs. nonchronically depressed individuals) and indicated significant impairment. The two groups only differed on the self-report measure BDI and the domains neuroticism and extraversion on the NEO-FFI with chronically depressed individuals obtaining higher BDI and neuroticism scores and lower extraversion scores.

Both groups benefited strongly from the inpatient stay experiencing a significant symptom reduction on all measures (HAMD 17, MADRS, BDI, GAF, SOFAS, CGI) and positive changes in all BIG FIVE personality domains (neuroticism, extraversion, openness to experience, tolerance, conscientiousness).

However, the recovery in the group of chronically depressed individuals was not as successful and achieved with greater effort. This was evident via a longer hospital stay, a greater variety of applied medication classes, lower remission rates, increased rates of suicidal ideation as well as

lower values on measures of depressive symptomatology (HAMD 17, MADRS) and social and occupational functioning (GAF, SOFAS, CGI) at discharge. Furthermore, a number of repeated measurement ANOVAS showed significant interaction effects indicating a slower rate of change for chronically depressed individuals compared to nonchronically depressed individuals (admission and discharge data: HAMD 17, MADRS, GAF, CGI; biweekly data: MADRS). In addition, individuals with chronic depression continued to obtain higher neuroticism scores and lower extraversion scores at discharge. The difference between the groups (HAMD 17) did not remain significant after one year though a trend in the same direction was visible.

The results indicate that the two groups of chronically and nonchronically depressed individuals share a number of characteristics in the acute phase of depression such as symptom severity. Individuals in the two groups also both experienced a significant symptom reduction in the course of their hospital stay which was focused on the treatment of depression. These findings underline the similarities of both groups who have both been assigned a diagnosis fom the category of affective disorders. It furthermore provides support for the findings summarized in the review of Kocsis (2003) and the meta-analyses of Cuijpers et al. (2010) as well as Negt et al. (2016) showing a general effectivenes of pharmacotherapy in the treatment of chronic depression even though the final treatment results were not fully satisfactory for 60% of individuals with chronic depression not reaching remission at discharge.

Simultaneously both groups differed on a number of significant factors indicating distinctive differences between the two groups. Individuals with chronic depression experienced a number of wearing factors to a stronger degree compared to nonchronically depressed individuals. The main impairment wasn't the acute severity of depressive symptoms. Depressive symptoms were similar in the groups of chronically and nonchronically depressed individuals in the acute phase when they were admitted to the hospital. The burden and thereby the specificity of chronic depression resulted from the persevering nature with which the symptoms persisted, ceasing at a slower rate compared to nonchronically depressed individuals while affecting all areas of life as was visible in reduced psychosocial functioning. The breadth of impairment which chronic depression claims from those affected was also apparent in the elevated rates of comorbidity (especially persistent somatoform pain disorders, abuse of sedatives and personality disorders) as

well as in higher levels of neuroticism and lower levels of extraversion exhibited by individuals with chronic depression compared to individuals with nonchronic depression in this study.

The study provides clear data documenting the extent of impairment experienced by chronically depressed individuals. It also highlights the path and the limits of improvements chronically depressed individuals achieve during inpatient treatment – a field of research which was formerly insufficiently examined as stated by Hölzel et al. (2011).

With respect to the hypothesis it can be stated that the findings described above provide overall support of the assumption that chronically depressed individuals experience greater levels of impairment compared to nonchronically depressed individuals. The impairment becomes apparent when taking into account the longer times individuals with chronic depression experience significant depressive symptoms as well as the breadth of impairment including reduced psychosocial functioning and comorbid illnesses. The impairment with respect to the absolute severity of depressive symptoms in the acute phase did not appear to differ between the two groups which might also be due to the inpatient sample with a high rate of double depression in the group of chronically depressed individuals.

The findings also support the hypothesis that individuals with chronic depression exhibit higher levels of neuroticism and lower levels of extraversion compared to individuals with nonchronic depression. These results replicate the findings of Wiersma et al. (2011) as well as Robison et al. (2009) with a large data sample. With respect to the relative relevance of the two factors the results highlight the role of extraversion which appeared to have a stronger predictive power compared to neuroticism. This result is in line with the findings of Wiersma et al. (2011) and Robison et al. (2009) and opposes the results reported by Hirschfeld et al. (1986) and Weissmann et al. (1978).

The results of the study furthermore replicate and expand the findings of Ormel et al. (2004) to the group of chronically depressed individuals. Ormel et al. (2004) demonstrated an influence of depressive symptomatology on personality traits for individuals with MDE. The change of personality traits along with a change of depressive symptomatology was apparent in both groups (chronic and nonchronic depression) via the significant reduction of neuroticism scores and significant elevation of scores of extraversion, openness to experience, tolerance, and

conscientiousness in the course of the inpatient stay along with the reduction of depressive symptomatology.

The reduced extraversion scores in the group of chronically depressed individuals compared to nonchronically depressed individuals even after discharge of an inpatient stay appears to be a very relevant factor to consider when diagnosing and treating individuals with chronic depression. It appears to require a particularly sensitive clinical environment to build a trusting relationship as a basis for gathering relevant information from individuals with chronic depression. The reduced positive, warm and assertive orientation towards others of chronically depressed individuals and their strong impairment based on the symptoms of depression have to be taken into account.

Furthermore the study results indicate that individuals with chronic depression have experienced a greater number of adverse childhood events compared to nonchronically depressed individuals. The results generally support the findings of Negele et al. (2015) and Wiersma et al. (2009). However, the current study was unable to validate the higher share of childhood trauma reported by Wiersma et al. (2009) in detail. Physical, psychological and sexual abuse as well as emotional neglect was not assessed separately with a specific instrument such as the Childhood Trauma Interview (Fink et al., 1995). The results on family-related childhood events such as separation of parents and parental loss were mixed, supporting the results of Wiersma et al. (2009) as well as Angst et al. (2009) to some extent without resulting in a clear pattern. Future research could further differentiate between the various forms of trauma and their predictive power for the development of chronic depression.

It was noteworthy that group differences with respect ot adverse childhood events were only found in the age category before the age of 6. This finding is an indicator for the fragility of early childhood and its relevance for the development of affective disorders in the future.

The data showing that individuals with chronic depression reported a lower age at onset as well as a longer latency between onset and first treatment compared to nonchronically depressed individuals stress the importance of sensitive diagnostic measures in health systems and timely psychotherapeutical and medical treatments as a crucial factor in order to reduce the probability of the development of a chronic depression after experiencing the first depressive episode.

The study did bear a number of inherent limitations. The analysis did not include any neurobiological measures such as oxytocin, which has been shown to play a role in the interpersonal impairments of chronically depressed individuals (Jobst et al., 2015). The study also did not include any measures of cognitive characteristics for which a small number of studies have found indications that they play a role in the development and maintenance of chronic depression (Wiersma et al., 2011; McCullough et al., 1994; Klein et al., 1988b). Due to the exploratory nature of the study, no correction for multiple tests was carried out. The disadvantage of this method lies in the increased risk of making a Type I error. The methodology was nonetheless chosen with the goal of optimizing the sensitivity of the analysis in order to receive indications of possible differences between the groups of chronically and nonchronically depressed individuals. A logistic regression was applied in order to gain insights regarding the strength of the differentiative power of the factors associated with chronic depression thereby correcting for the multiple univariate tests.

Taking into account the limitations the results nonetheless show that individuals with chronic depression differ clearly on a significant number of characteristics from individuals with nonchronic depression. These findings indicate that chronicity is a clinically meaningful factor thereby supporting the current body of research (e.g. Hölzel et al., 2011).

The differences between the groups of chronically and nonchronically depressed individuals apparent in the study data might also be an indication of the diversity of factors relevant within the group of chronically depressed individuals. The higher rates of comorbid diagnoses of neurotic, stress-related and somatoform disorders and hereby more often the diagnosis of a persistent somatoform pain disorder indicate the possibility that chronic depression can be at least in part be influenced or triggered by the experience of a chronic medical condition.

Chronic depression does appear to constitute a separate phenomenon which differs significantly from nonchronic depression on key dimensions. This study was not laid out to investigate whether chronic depression comprises a distinct form or an additional key dimension of depression as was proposed by Klein (2008a). The fact that no significant differences were found between the groups with respect to a family history of affective disorders and the result that the depressive symptomatology at intake was similar in the two groups, however, supports the assumption by Klein (2008a) that chronicity along with severity constitutes a key feature of

depression and that chronic depression is not a distinct illness. More research is needed to clarify this question.

The results show the importance of differentiating between the two groups in the clinical context. Identifying individuals with chronic depression at the beginning of treatment is relevant for managing expectations for both doctors and patients since chronicity has a strong impact on the clinical course. It is also a relevant information for choosing and evaluating the effect of treatment options. The reduced extraversion scores of chronically depressed individuals make it more difficult to correctly detect the crucial clinical factor of chronicity and to then adequately allocate significant resources to the respective patients. This finding should encourage clinical practitioners to meticulously assess and examine the clinical history of their depressed patients for signs of chronicity and to focus also on depressed individuals who appear especially introverted.

Overall, the results stress the importance of identifying chronically depressed patients reliably in order to guide treatment selection and expectations. They also amplify the relevance of early diagnosing and treating patients with depression in order to avoid a chronic course where possible. In addition, the results demonstrated that depression is not an interminable illness and that both chronically and nonchronically depressed patients benefit strongly from inpatient treatment.

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10 Appendix

Table 8. Clinical characteristics at admission

Characteristic	Total sample n (%)/ mean (± SD)	Chronic depression n (%)/ mean (± SD)	Nonchronic depression n (%)/ mean (± SD)	p[1]
Affective disorder diagnosis (ICD 10: F3), n (%)				
Mild (32.0, F33.0)	20 (2.1)	3 (2.7)	17 (2.0)	.72
Moderate (32.1, F33.1)	325 (34.1)	29 (25.7)	296 (35.2)	.045
Severe (32.2, F32.3, F33.2, F33.3)	596 (62.5)	76 (67.3)	520 (61.8)	.30
Dysthymia (F34.1)	57 (6.0)	57 (50.4)	-	-
Recurrent depression (F33.0 – F33.9)	525 (55.0)	65 (57.5)	460 (54.7)	.62
Psychotic depression (F33.3.,F32.3.,F31.5)	82 (8.6)	6 (5.3)	76 (9.0)	.21
Mental and behavioral disorders due to psychoactive substance abuse (ICD10: F1), n (%)[2]	103 (10.8)	18 (15.9)	85 (10.1)	.074
Alcohol (F10)	79 (8.3)	11 (9.7)	68 (8.1)	.58
Cannabinoids (F12)	7 (.7)	-	7 (.8)	1
Sedatives or hypnotics (F13)	16 (1.7)	6 (5.3)	10 (1.2)	<.01
Multiple drug use and use of other psychoactive substances (F19)	4 (.4)	1 (.9)	3 (.4)	.40
Neurotic, stress-related and somatoform disorders (ICD10: F4) , n (%)[2]	114 (11.9)	21 (18.6)	93 (11)	.029
Phobic anxiety disorders (F40)	58 (6.1)	11 (9.7)	47 (5.6)	.093
Agoraphobia (F40.0)	36 (3.8)	5 (4.4)	31 (3.7)	.60
Social phobias (F40.1)	19 (2.0)	5 (4.4)	14 (1.7)	.063
Specific phobias (F40.2)	9 (.9)	2 (1.8)	7 (.8)	.29
Other anxiety disorders (F41)	30 (3.1)	3 (2.7)	27 (3.2)	1
Panic disorder (F41.0)	29 (3.0)	2 (1.8)	27 (3.2)	.76
Generalized anxiety disorder (F41.1)	3 (.3)	1 (.9)	2 (.2)	.31
Obsessive-compulsive disorder (F42)	10 (1.0)	1 (.9)	9 (1.1)	1
Reaction to severe stress, and adjustment disorders (F43)	5 (.5)	-	5 (.6)	1
Post-traumatic stress disorder (F43.1)	5 (.5)	-	5 (.6)	1
Somatoform disorders (F45)	26 (2.7)	7 (6.2)	19 (2.3)	.026
Somatization disorder (F45.0)	3 (.3)	1 (.9)	2 (.2)	.32
Undifferentiated somatoform disorder (F45.1)	7 (.7)	-	7 (.8)	1
Persistent somatoform pain disorder (F45.4)	17 (1.8)	7 (6.2)	10 (1.2)	<.01

Table 8. Clinical characteristics at admission

Characteristic	Total sample n (%)/ mean (± SD)	Chronic depression n (%)/ mean (± SD)	Nonchronic depression n (%)/ mean (± SD)	p[1]
Number of comorbid psychiatric disorders (ICD10), n (%)				<.001
0	675 (70.8)	62 (54.9)	613 (72.9)	
1	190 (19.9)	32 (28.3)	158 (18.8)	
2	57 (6.0)	15 (13.3)	42 (5.0)	
3	24 (2.5)	4 (3.5)	20 (2.4)	
≥ 4	8 (.8)	0 (0)	8 (1.0)	
Number of comorbid psychiatric disorders (ICD10), mean (±SD)	.43 (.79)	.65 (.84)	.40 (.77)	<.01
HAMD 17, mean (±SD)	22.4 (6.0)	22.7 (6.0)	22.3 (6.0)	.50
MADRS, mean (±SD)	29.9 (7.6)	30.0 (7.9)	29.9 (7.5)	.92
BDI, mean (±SD)	25.7 (10.8)	28.2 (10.9)	25.3 (10.8)	.024
CGI, mean (±SD)	5.2 (.7)	5.3 (.7)	5.2 (.7)	.36
SOFAS, mean (±SD)	49.8 (13.4)	48.0 (13.8)	50.0 (13.3)	.15
GAF, mean (±SD)	47.9 (11.6)	48.2 (12.7)	47.9 (11.5)	.82

[1]Comparisons between nonchronic and chronic depressed persons, using Fisher tests for categorical variables and t-tests for continuous variables. [2]Only categories shown with more than 2 observed cases.

Table 9. Change in clinical and personal characteristics between admission and discharge

	Admission				Discharge				Repeated Measurement ANOVA[1]		
Characteristic	Total sample	Chronic Depress.	Non-chronic Depress.		Total sample	Chronic Depress.	Non-chronic Depress.		Effects		
	n (%)/ mean (± SD)			p	n (%)/ mean (± SD)			p	Interaction	Time	Group
HAMD 17, mean ± SD	22.3 (6.1)	22.7 (6.3)	22.2 (6.1)	.51	7.5 (5.5)	10.3 (6.5)	7.1 (5.3)	<.001	<.01	<.001	.048
MADRS, mean ± SD	29.6 (7.5)	29.7 (8.1)	29.5 (7.4)	.83	10.1 (8.0)	14.6 (9.4)	9.5 (7.6)	<.001	<.001	<.001	.82
BDI, mean ± SD	24.9 (10.6)	29.3 (9.7)	24.4 (10.6)	<.01	10.9 (9.1)	12.4 (9.7)	10.7 (9.0)	.24	.073	<.001	<.01
CGI, mean ± SD	5.2 (.7)	5.3 (.7)	5.2 (.7)	.19	2.8 (1.2)	3.5 (1.3)	2.8 (1.2)	<.001	<.001	<.001	.36
SOFAS, mean ± SD	50.3 (13.4)	49.4 (13.4)	50.4 (13.4)	.50	68.5 (11.6)	65.0 (12.1)	68.9 (11.5)	<.01	.064	<.001	.47
GAF, mean ± SD	48.2 (11.6)	49.2 (12.4)	48.1 (11.5)	.43	70.0 (11.4)	65.5 (12.1)	70.6 (11.1)	< .001	<.001	<.001	.30
NeoFFI, mean ± SD											
Neuroticism	2.6 (.6)	2.8 (.6)	2.6 (.6)	.014	2.2 (.7)	2.5 (.7)	2.2 (.7)	<.01	.68	<.001	.015
Extraversion	1.7 (.5)	1.5 (.5)	1.8 (.5)	<.01	1.9 (.5)	1.7 (.5)	2.0 (.5)	<.01	.74	<.001	<.01
Openness to experience	2.2 (.5)	2.2 (.6)	2.2 (.5)	.78	2.3 (.5)	2.4 (.6)	2.3 (.5)	.55	.26	<.01	.76
Tolerance	2.5 (.4)	2.4 (.5)	2.5 (.4)	.31	2.6 (.4)	2.5 (.4)	2.6 (.4)	.45	.71	<.01	.28
Conscientiousness	2.4 (.6)	2.4 (.6)	2.4 (.6)	.43	2.6 (.5)	2.6 (.6)	2.6 (.5)	.75	.52	<.001	.36

Table 9. Change in clinical and personal characteristics between admission and discharge

	Admission				Discharge				Repeated Measurement ANOVA[1]		
Characteristic	Total sample	Chronic Depress.	Non-chronic Depress.		Total sample	Chronic Depress.	Non-chronic Depress.		Effects		
	n (%)/ mean (± SD)			p	n (%)/ mean (± SD)			p	Interaction	Time	Group
Suicidal tendency (HAMD item 3), n (%)				.15				<.001			
Absent	175 (22.8)	18 (19.6)	157 (23.3)		660 (86.0)	65 (70.7)	595 (88.1)				
Feels life is not worth living	198 (25.8)	30 (32.6)	168 (24.9)		73 (9.5)	16 (17.4)	57 (8.4)				
Whishes he were dead	177 (23.1)	18 (19.6)	159 (23.6)		26 (3.4)	9 (9.8)	17 (2.5)				
Suicidal ideas	119 (15.5)	19 (20.7)	100 (14.8)		6 (.8)	2 (2.2)	4 (.6)				
Suicidal attempts	98 (12.8)	7 (7.6)	91 (13.5)		2 (.3)	0	2 (.3)				
Depression Severity (based on HAMD17), n (%)				.51				<.001			
Remission (≤ 7)	4 (.5)	1 (1.1)	3 (.4)		456 (59.5)	36 (39.1)	420 (62.2)				
Mild (7 < x < 14)	48 (6.3)	5 (5.4)	43 (6.4)		211 (27.5)	32 (34.8)	179 (26.5)				
Moderate (14 ≤ x < 19)	170 (22.2)	17 (18.5)	153 (22.7)		59 (77)	9 (9.8)	50 (7.4)				
Severe (≥ 19)	545 (71.1)	69 (75.0)	476 (70.5)		41 (5.3)	15 (16.3)	26 (3.9)				

[1]Where applicable.

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12 Declaration of Authorship

Eidesstattliche Versicherung

Kolter, Miriam

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema

Characteristics of chronic depression before, during and after inpatient treatment

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

Fürth, 27.11.2019	Miriam Kolter
Ort, Datum	Unterschrift Doktorandin